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Second Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency and Information Dossiers on Substances Designated

TSCA Interagency Testing Committee, Washington, D.C.

Prepared for

National Science Foundation, Washington, D.C.

Apr 78

United States
Environmental Protection
Agency

Office of
Toxic Substances
Washington, DC 20460

April 1978

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Toxic Substances

EPA

Second Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency

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SECOND REPORT OF THE TSCA INTERAGENCY TESTING COMMITTEE

TO THE

ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

APRIL 1978

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TOXIC SUBSTANCES CONTROL ACT
INTERAGENCY TESTING COMMITTEE

722 Jackson Place, N.W.
Washington, D.C. 20006

Member Agencies

Council on Environmental Quality
Department of Commerce
Environmental Protection Agency
National Cancer Institute
National Institute of Environmental Health Sciences
National Institute for Occupational Safety and Health
National Science Foundation
Occupational Safety and Health Administration

Liaison Agencies

Consumer Product Safety Commission
Department of Defense
Department of the Interior
Food and Drug Administration

April 10, 1978

Honorable Douglas M. Costle
Administrator
Environmental Protection Agency
Washington, D.C. 20460

Dear Mr. Costle:

In accordance with the requirements of the Toxic Substances Control Act, the TSCA Interagency Testing Committee is now recommending the addition of eight designated entries to the Section 4(e) Priority List. These revisions and the Committee's reasons for recommending them are presented in the enclosed document entitled, "Second Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency." The representatives of the statutory member agencies are in consensus on these revisions.

Also, the report contains two special recommendations which bear on the activities of the Environmental Protection Agency. First, it is recommended that EPA consider taking the initiative in the development of a comprehensive survey of health and environmental effects testing facilities in the United States. And second, your agency is encouraged to join in the effort to provide increased training support in the fields of mammalian and environmental toxicology, pathology, occupational health and epidemiology as these fields relate to the need for greater numbers of qualified personnel to meet the increasing demand for testing.

1.c

The Committee has not yet completed its review of all of those chemical substances and categories of substances identified during our initial activities in 1977. This review is to continue and will be a subject of future Committee reports. In addition, candidate chemicals recommended by the Committee members or public comment will be reviewed by the Committee as such information is made available.

We trust that this report will be of value to EPA as it continues to carry out the Toxic Substances Control Act.

Sincerely,

Marvin E Stephenson

Marvin E. Stephenson
Chairperson
TSCA Interagency Testing Committee

Enclosure

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SECOND REPORT
OF THE
TSCA INTERAGENCY TESTING COMMITTEE
TO THE
ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

APRIL 1978

1.e

TSCA INTERAGENCY TESTING COMMITTEE

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ENVIRONMENTAL PROTECTION AGENCY

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NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

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1·F

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Executive Secretary: Carol A. Mapes

Secretary: Phyllis D. Tucker

ACKNOWLEDGEMENTS

The Committee wishes to acknowledge the important contributions of the many individuals and groups who have significantly aided us in our work. These include:

-- the Federal agencies who have cooperated by providing support through the liaison members;

-- Clement Associates, Inc., technical support contractor;

-- the National Science Foundation, for funding and managing the technical support contract and the National Institute of Environmental Health Sciences, for assisting in that funding;

-- former Committee members:
    Sidney R. Galler, Department of Commerce
    William M. Upholt, Environmental Protection Agency
    Norbert P. Page, National Institute for Occupational Safety and Health
    Grover C. Wrenn, Occupational Safety and Health Administration

-- EPA staff members who assisted the Committee in a variety of activities, and particularly:
    Donald G. Barnes, Office of Toxic Substances
    John W. Lyon, Office of General Counsel
    Ralph C. Northrop, Jr., Office of Toxic Substances

-- the numerous experts who prepared presentations and materials for the Committee; and

-- the many individuals and organizations who responded to the Committee's Initial Report to the Administrator, Environmental Protection Agency.

SUMMARY

A central provision of the Toxic Substances Control Act (TSCA, P.L. 94-469) concerns the testing of chemical substances and mixtures which are used in commerce or may represent an unreasonable risk of injury to human health or the environment. The Act provides for continuing advice from certain Federal agencies having common interests in identifying chemical substances or mixtures for testing. Accordingly, the TSCA Interagency Testing Committee, which is composed of representatives from those concerned Federal agencies, regularly provides to the Administrator of the Environmental Protection Agency (EPA) recommendations on chemicals and mixtures to which the Administrator should give priority consideration for the promulgation of testing rules.

As a result of its deliberations during the past six months, the Committee has elected to revise the TSCA Section 4(e) Priority List by the addition of four individual substances and four categories of substances. The Committee considers these additions to be of the same priority as the previously designated entries. The chemical substances or categories being designated for addition to the Priority List and the testing recommendations are presented alphabetically as follows:

Substance or Category	Testing Recommended
Acrylamide	Carcinogenicity, mutagenicity, teratogenicity, environmental effects and epidemiological study.
Aryl Phosphates	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, environmental effects and epidemiological study
Chlorinated Naphthalenes	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, environmental effects and epidemiological study
Dichloromethane	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, environmental effects, and epidemiological study

Halogenated Alkyl Epoxides	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, and epidemiological study
Polychlorinated Terphenyls	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, and environmental effects
Pyridine	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, environmental effects, and epidemiological study
1,1,1-Trichloroethane	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, and epidemiological study

A set of dossiers containing information on the additional entries designated to the Priority List will be forwarded to the EPA Administrator within a few weeks.

SECOND REPORT
OF THE
TSCA INTERAGENCY TESTING COMMITTEE
TO THE
ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

APRIL 1978

CHAPTER 1. INTRODUCTION

1.1 Committee Establishment and Responsibilities

The Toxic Substances Control Act (P.L. 94-469) establishes the TSCA Interagency Testing Committee under Section 4(e). The Committee has the continuing responsibility to identify and recommend to the Administrator of the Environmental Protection Agency (EPA) chemical substances or mixtures which should be tested to determine their hazard to human health or the environment. The statute requires that the Committee consider revisions to its previous recommendations at least every six months.

The Committee has eight statutory members appointed by the Federal agencies identified for membership in Section 4(e)(2)(A) of the Act, a number of alternate members as permitted by Section 4(e)(2)(B)(i), and liaison members from several Federal agencies with programs related to the control of toxic substances. Current Committee members, alternates, and liaison representatives are identified at the beginning of this report.

1.2 Initial Report

In July 1977, the Committee published a Preliminary List of 330 chemical substances and categories of such substances including background information describing the methods used by the Committee in making those selections [Reference No. 1]. The Preliminary List contains substances and categories selected primarily on the basis of their potential for human exposure and environmental release. Subsequently, the chemicals on the Preliminary List and chemicals added to the Preliminary List on the basis of public comments and Committee recommendations were screened further by the Committee. The screening process was based primarily on the chemicals' potential for causing adverse human and/or environmental effects but also considered their exposure potential. Available data on these chemicals were reviewed with regard to: potential for carcinogenic, mutagenic, teratogenic, and chronic toxic effects; their ability to bioaccumulate or cause deleterious environmental effects; and possible toxic impurities. A scoring system was used in this process which took into account both available information and the lack of it for these factors. The Committee further narrowed the list of substances and categories under consideration on the basis of its scientific judgment and the scoring results, and requested its technical contractor to prepare dossiers on these chemicals. The Committee was able to review about one-half of these substances and categories aided by information in the dossiers. Four individual chemicals and six categories of chemical substances were selected for inclusion in the Initial Report to the Administrator, Environmental Protection Agency [Reference No. 2] dated October 1, 1977.

In addition to the listing of the chemicals designated by the Committee for consideration by EPA, the report contains a detailed description of the methods used in developing the Committee's initial recommendations including data sources and methods used for production, release and exposure scores, as well as biological and environmental scores. Later, on February 7, 1978, a finalized set of supporting dossiers on the designated entries on the Priority List was officially transmitted to the Administrator.

1.3 Committee Activities During This Reporting Period

Since completion of its initial recommendations in October 1977, the Committee has continued to consider individual chemical substances and mixtures identified for in-depth consideration by the screening process mentioned in the preceding section.

This review has given specific consideration to the factors described in TSCA Section 4(e)(1)(A) and other relevant factors identified by the Committee. Readily available information on these factors and the knowledge and professional judgment of the Committee members have been employed to select additional entries to the TSCA Section 4(e) Priority List. On the basis of the review of more, but not all, of the previously requested dossiers, the Committee is now recommending the addition of four chemical substances and four categories of chemical substances to the 4(e) Priority List.

1.4 Future Activities of the Committee

In the course of developing its third report, the Committee expects to continue reviewing those dossiers in hand and consider new dossiers on additional chemicals and groups.

CHAPTER 2. CONSIDERATION OF AVAILABILITY OF TESTING FACILITIES AND PERSONNEL

Section 4(e)(1)(A) of TSCA requires that the Committee consider, among other factors, the reasonably foreseeable availability of facilities and personnel for carrying out the testing on the substances or mixtures recommended to the Administrator for priority consideration. The Committee concludes that testing capabilities are presently adequate to carry out the recommended health effects and environmental tests on the chemicals listed in Table 1. However, the concerns expressed by the Committee in its first report [Reference No. 2, p.55048] regarding the limited national capability for conducting long-term tests for environmental effects are reiterated.

The expansion of testing facilities by industry, contracting laboratories, and universities seems to be proceeding at a satisfactory rate, especially in the area of health effects testing. Estimates indicate a significant increase in facilities over the next five years. While this is encouraging, the Committee is aware that the increasing requirements of various government agencies are creating competition for the same testing facilities and personnel. Therefore, the projected need and capacity for health and environmental effects testing is somewhat uncertain and should be more accurately surveyed. The Committee recommends that EPA assume the leadership in the development of a comprehensive survey of availability of current Federal and private health effects testing facilities in the United States and the projected annual capacity of such facilities during the next five years. In those cases where testing is likely to involve animal bioassay, the survey should include an evaluation of the capacity to provide appropriate and sufficient populations of test species.

Of paramount concern to the Committee is the availability of qualified personnel. All indices contained in the Report of the Second Task Force for Research Planning in the Environmental Health Sciences [Reference No. 3] indicate a current and future shortage of research professionals in the fields of mammalian and environmental toxicology, pathology, occupational health, and epidemiology. There will be a dearth of professionals and supporting technical personnel in these various skills for many years unless increased training efforts occur at the national level. The Committee notes that several Federal agencies are involved in augmenting training support and recommends that EPA join in these efforts in a significant way.

There is also a need to maintain viable basic research programs in toxicology and other related health fields. This basic need should not be neglected in order to assure short-term gains in the practical application of the present state of the art. Because of the interdisciplinary nature of toxicology and environmental health research, the educational training for some of the disciplines can be provided only by facilities with personnel engaged in this type of research.

The Committee believes that the Civil Service Commission could do much to stimulate interest in these professions by creating professional series and registers for such scarce categories as toxicologists, pathologists, epidemiologists and other scientific fields in environmental protection. Recognition of these environmental health professions by the Commission could encourage students to investigate careers in fields thus far hidden as Federal employment opportunities. It is concluded that such an action by the Commission would have the effect of increasing the available scientific manpower in these speciality fields both in the Government and in industry where the demand for such personnel exists.

CHAPTER 3. RECOMMENDATIONS OF THE COMMITTEE

3.1 Substances and Categories of Substances Recommended for Testing

On the basis of the review and evaluation of chemical substances which was carried out according to the methods and procedures described in Sections 1.2 and 1.3, the Committee is revising the TSCA Section 4(e) Priority List to add certain substances and categories of substances for which specific testing is recommended. The Priority List and the date each item was placed on the List are given in Table 1. The testing recommendations and reasons for such recommendations are indicated in Section 3.2 for the new entries. Supporting dossiers of information are being prepared in final form and will be forwarded to the Administrator, EPA, at an early date.

All additions to the List are designated chemical substances and categories of chemical substances which the Committee has determined require the Administrator's action under TSCA Section 4(a) within twelve months. The Committee considers these additions to be of the same priority as the previously designated entries. In recommending a category of chemical substances for testing (e.g., the aryl phosphates), the Committee recognizes that certain chemicals which are members of the category may have been tested previously for an effect of concern. For those chemicals no additional testing may be warranted if the results of previously completed tests are judged adequate for assessing the effect of concern. The Committee also recognizes that the definition and inclusive limits of a given listed category of substances may require additional specification or change in specification as the testing rule is developed. Unless stated otherwise, the chemical substance recommended for testing should be the product to which the population is exposed.

3.2 Reasons for Recommending Testing of the Additional Substances and Categories of Substances

In accordance with the reporting requirements of the Act, the Committee has listed in the following sections the test recommendations and reasons for recommending testing for those entries being placed on the Priority List at this time. Table 2 presents a summary of the testing recommendations for each addition to the List.

Table 1. THE TSCA SECTION 4(e) PRIORITY LIST, BY ALPHABETICAL ARRANGEMENT

Designated Entry	Date of Entry
Acrylamide	April 1978
Alkyl Epoxides	October 1977
Alkyl Phthalates	October 1977
Aryl Phosphates	April 1978
Chlorinated Benzenes, Mono- and Di-	October 1977
Chlorinated Naphthalenes	April 1978
Chlorinated Paraffins	October 1977
Chloromethane	October 1977
Cresols	October 1977
Dichloromethane	April 1978
Halogenated Alkyl Epoxides	April 1978
Hexachloro-1,3-Butadiene	October 1977
Nitrobenzene	October 1977
Polychlorinated Terphenyls	April 1978
Pyridine	April 1978
Toluene	October 1977
1,1,1-Trichloroethane	April 1978
Xylenes	October 1977

Table 2. SUMMARY OF TESTING RECOMMENDATIONS BY THE TSCA INTERAGENCY TESTING COMMITTEE

Substance or Category	Carcinogenicity	Mutagenicity	Teratogenicity	Other Chronic Effects	Environmental Effects	Epidemiology Study
Acrylamide	X	X	X		X	X
Aryl Phosphates	X	X	X	X	X	X
Chlorinated Naphthalenes	X	X	X	X	X	X
Dichloromethane	X	X	X	X	X	X
Halogenated Alkyl Epoxides	X	X	X	X		X
Polychlorinated Terphenyls	X	X	X	X	X	
Pyridine	X	X	X	X	X	X
1,1,1-Trichloroethane	X	X	X	X		X

3.2.A ACRYLAMIDE

TESTING RECOMMENDATIONS:

- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Environmental Effects
- Epidemiology

SUBSTANCE IDENTIFICATION: CAS NO. 79-06-1

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: The 1976 U.S. production of acrylamide monomer is estimated at 64 million pounds, and indications point to a high growth rate of around 12 percent for the next decade. Eighty percent of the acrylamide produced is used captively in polymer production for water treatment, papermaking and wastewater clarification. About 5 percent is used in chemical grouts as the acrylamide monomer, for soil stabilization and sewer rehabilitation. The remainder is consumed in other chemical syntheses. Other uses are in the paper and paperboard industry, coal industry, mining and ore benefication industry, and secondary oil recovery industry.

Acrylamide release to the environment (usually ending up in surface and ground water) occurs at manufacturing sites, soil grouting sites, polymer application sites and in handling. General population, low-level exposure to acrylamide is likely to occur wherever polyacrylamides are utilized. No data are available on release rates into the environment or actual concentration levels. NIOSH estimates that 20,000 workers are potentially exposed in the workplace.

Carcinogenicity: Acrylamide has not been tested for carcinogenicity. Because of widespread low-level exposure to the population, acrylamide should be tested for carcinogenicity.

Mutagenicity: Although the results of two independently reported Ames tests were negative, the Committee believes that additional tests, employing other systems, are required to evaluate the mutagenic potential of this chemical.

Teratogenicity: Transplacental transport of acrylamide was demonstrated in rats; therefore, it should be tested conclusively for teratogenicity.

Environmental Effects: In view of the high degree of neurotoxicity and neuropathy caused by cumulative exposure and the extensive use of this material in waste water treatment and soil grouting, studies should be initiated to determine the degree of leaching of the monomer from the polymer with water and various solvents. Further, the potential for environmental exposures to the aquatic ecosystem, movement in soil solution and leachate from soil waste must be determined for biological effects on plant and animal life.

Epidemiology: No epidemiological reports on acrylamide have been found in the literature. Studies are needed to provide information on human exposure to acrylamide and to determine the relationship between airborne concentrations and observed effects on humans.

3.2.B ARYL PHOSPHATES

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Environmental Effects
Epidemiology

CATEGORY IDENTIFICATION: This category consists of phosphate esters of phenol or of alkyl-substituted phenols. Tri-aryl and mixed alkyl and aryl esters are included, but tri-alkyl esters are excluded.

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: As a category, the aryl phosphates are produced in quantities exceeding 65 million pounds/year. Several individual aryl phosphates, such as tritolyl phosphate and triphenyl phosphate, have annual production greater than 10 million pounds. Aryl phosphates are widely used as plasticizers in polymers (principally in polyvinyl chloride) and in hydraulic fluids and high pressure lubricants. Such uses provide opportunity for extensive occupational exposure to these compounds beyond that encountered in their manufacture. NIOSH estimates that over 2 million workers are so exposed. Because of the nature of their uses, most of the aryl phosphates manufactured will ultimately be released into the environment, although those used as plasticizers may be released quite slowly. Persistence of aryl phosphates in the environment for significant periods (at least on the order of months) is indicated by the available data.

Carcinogenicity: With the exception of several tests of inadequate duration using triphenyl phosphate, the carcinogenic potential of aryl phosphates has not been assessed. Carcinogenicity testing should be performed on aryl phosphates having substantial human exposure and/or environmental release.

Mutagenicity: No mutagenicity testing has been reported for aryl phosphates. Such testing should be performed because of the potential of these substances for widespread environmental release and human exposure.

Teratogenicity: No teratogenicity testing has been reported for aryl phosphates. Such testing should be conducted for aryl phosphates having substantial human exposure and/or environmental release.

Other Chronic Effects: The neurotoxicity of certain aryl phosphates is well documented. The Committee recommends that aryl phosphates be tested for chronic effects with special emphasis on neurotoxic activity.

Environmental Effects: Available data, although limited, indicate a potential for persistence of aryl phosphates in the aquatic environment, as well as a potential for their bioaccumulation in aquatic species. There is evidence of chronic toxicity of aryl phosphate hydraulic fluids to fish. Several aryl phosphates potentiate the toxic effects of organophosphate pesticides on insects and one (tri-o-cresyl phosphate) has been shown to potentiate such effects in non-target organisms including mammals. In view of this, the environmental fate and effects on aquatic and terrestrial systems should be evaluated for aryl phosphates.

Epidemiology: Because of the large-scale production and potential for substantial occupational exposure of certain aryl phosphates, the Committee recommends that epidemiological studies be conducted.

3.2.C CHLORINATED NAPHTHALENES

TESTING RECOMMENDATIONS:

- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Other Chronic Effects
- Environmental Effects
- Epidemiology

CATEGORY IDENTIFICATION: This category consists of chlorinated derivatives of naphthalene (empirical formula $C_{10}H_xCl_y$, where $x+y=8$).

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: Available data indicate a production volume on the order of millions of pounds annually. These products have both moderately dispersive uses (e.g., lubricating and cutting oil additives) and enclosed uses (e.g., dielectric for automotive capacitors). Although NIOSH has estimated that several thousand workers are exposed to these compounds, little is known about the ultimate release of these materials from the workplace, during product use, or as a result of disposal.

Health Effects: Animal studies and analysis of human exposure reveal that these compounds are biologically active, with reports of dermatological (e.g., chloracne) and systemic (liver) effects. To date, there are no reported data on the carcinogenicity, mutagenicity, or teratogenicity of these compounds. Thus, there is a need to conduct such studies, as well as to investigate more thoroughly the chronic effects of these materials. Epidemiological studies should be undertaken where appropriate.

Environmental Effects: Little information on the ecological effects of these materials is available, but the detection of chlorinated naphthalenes in stream sediments, fish, and fish-eating birds points to their dispersal, persistence, and bioaccumulation in the food chain. Therefore, testing is needed to obtain data for judging the environmental effects of these chemicals.

3.2.D DICHLOROMETHANE

TESTING RECOMMENDATIONS:

- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Other Chronic Effects
- Environmental Effects
- Epidemiology

SUBSTANCE IDENTIFICATION: CAS NO. 75-09-2

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: The 1976 U.S. production of dichloromethane (also known as methylene chloride) exceeded 500 million pounds, a 12 percent increase over the 1972 level. An average 9 percent annual growth rate is projected over the next several years as this chemical enters markets dominated by fluorochlorocarbons in the past. Approximately 3/4 of the volume produced is thought to be released to the environment through activities at industrial sites, in homes and elsewhere. NIOSH estimated that 2.5 million workers are exposed to this material at their place of work. Its use in an array of aerosol spray products and other household products brings a large fraction of the general population into contact with this chemical.

Carcinogenicity: No carcinogenicity test data were found in the searched literature. There is sufficient concern for the Committee to recommend this chemical for such testing. The Committee is aware of two studies currently under way, however, whose results may be judged adequate to obviate the need for additional testing.

Mutagenicity: No mutagenicity test data have been reported. Such studies should be conducted in view of the widespread exposure to this chemical and its demonstrated biological activity.

Teratogenicity: One study has reported equivocal findings of abnormalities in the offspring of pregnant rats and mice exposed to this chemical. Additional testing is needed to assess this potential hazard.

Other Chronic Effects: Laboratory investigations and case studies have reported that dichloromethane can affect various organs (e.g., lungs and eye) and systems (blood), as well as behavior. Given the widespread use of this chemical under many different conditions, this information indicates a need for further testing.

Environmental Effects: Dichloromethane is being released in large quantities and in a broad dispersion pattern throughout the environment. Low-level residues have been measured in water. The exact nature of this exposure and its chronic effects on the biota need to be determined.

Epidemiology: Epidemiological studies should be conducted to assess human risk.

3.2.E HALOGENATED ALKYL EPOXIDES

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Epidemiology

CATEGORY IDENTIFICATION: This category consists of halogenated noncyclic aliphatic hydrocarbons with one or more epoxy functional groups.

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: The 1975 U.S. production of epichlorohydrin (1-chloro-2,3-epoxypropane) exceeded 500 million pounds. NIOSH estimates that between 50,000 and 140,000 workers are exposed to epichlorohydrin annually. While epichlorohydrin is currently the only widely used halogenated alkyl epoxide, advertising and trends in the chemical industry lead the Committee to the conclusion that chemicals of this type may find wider use in the future.

Carcinogenicity: Halogenation of an alkyl epoxide enhances its activity as an alkylating agent and hence its biological activity. Halogenated alkyl epoxides also may inhibit detoxifying enzymes in mammals. Equivocal results of recent carcinogenicity studies on epichlorohydrin further point out the need for testing this chemical category for potential carcinogenicity.

Mutagenicity: Epichlorohydrin has been shown to be mutagenic to mice and bacteria. The potential human toxicity of this and other halogenated alkyl epoxides should be evaluated.

Teratogenicity: No information could be found on the potential for teratogenicity of the halogenated alkyl epoxides and they should be studied for this effect.

Other Chronic Effects: Epichlorohydrin has been reported to penetrate human skin and cause systemic effects. This raises concern for other toxic effects and target organ toxicity of all the halogenated alkyl epoxides. Appropriate studies for these effects are recommended.

Epidemiology: No epidemiological studies of any of the halogenated alkyl epoxides were found in the literature. Studies are needed to provide information on the effects of human exposure to these compounds.

3.2.F POLYCHLORINATED TERPHENYLS

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Environmental Effects

CATEGORY IDENTIFICATION: This category consists of the polychlorinated *ortho*-, *meta*- and *para*-terphenyls.

REASONS FOR RECOMMENDATIONS:

Production, Release and Exposure: Although the production of polychlorinated terphenyls was discontinued in the United States in 1972, there has been an increase in imports of polychlorinated terphenyls from 160,000 pounds in 1973 to 400,000 pounds in 1975. Polychlorinated terphenyls are presently used in waxes for investment casting and this use leads to wide environmental dispersion. Residues of polychlorinated terphenyls have been found in human fat and milk and in samples of water and sludge. In a group of 27 individuals tested for blood levels of polychlorinated terphenyls and polychlorinated biphenyls, the average concentration of polychlorinated terphenyls in the blood was greater than that of polychlorinated biphenyls, despite a far greater industrial use of polychlorinated biphenyls in the area of study.

Carcinogenicity: No reports of long-term carcinogenicity studies of polychlorinated terphenyls were found in the searched literature. The Committee recommends that polychlorinated terphenyls be tested for carcinogenicity.

Mutagenicity: No information on the mutagenicity of polychlorinated terphenyls was found in the searched literature. The Committee recommends that mutagenicity tests be conducted.

Teratogenicity: No information on the teratogenicity of polychlorinated terphenyls was found in the searched literature. The Committee recommends that teratogenicity tests be conducted.

Other Chronic Effects: Liver, skin and hematopoietic effects have been observed at high level exposures. Effects at lower levels cannot be characterized from existing data. Chronic studies to evaluate the effects of prolonged exposures are recommended.

Environmental Effects: The limited available data indicate a potential for bioaccumulation. No adequate information is available on the ecological effects of these chemicals.

3.2.G PYRIDINE

TESTING RECOMMENDATIONS:

- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Other Chronic Effects
- Environmental Effects
- Epidemiology

SUBSTANCE IDENTIFICATION: CAS No. 110-86-1

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: The annual production of pyridine is estimated to be in excess of 60 million pounds, based on production amounts for 1976. Although the amount of pyridine released into the environment is unknown, its production volume and variety of uses raise concern with respect to human exposure. NIOSH estimates that 249,000 workers may be exposed to pyridine.

Carcinogenicity: Only one limited carcinogenicity study was found in the searched literature. By current standards, the study is judged inadequate as an evaluation of the carcinogenic potential of pyridine. The Committee, therefore, recommends that appropriate carcinogenicity testing be undertaken on pyridine.

Mutagenicity: No mutagenicity studies on pyridine were found in the searched literature. Given its known biological activity, production volume, and human exposure, it is recommended that appropriate mutagenicity testing be undertaken on pyridine.

Teratogenicity: Only one limited teratogenicity study was found in the searched literature on pyridine. It indicated that pyridine produced abnormalities in chicken embryos. An evaluation of teratogenic effects should be undertaken in other species.

Other Chronic Effects: The carcinogenicity study cited above is the only investigation lasting one year or longer found in the searched literature on the possible chronic effects of pyridine. Short-term studies indicate that pyridine affects the central nervous system and causes degeneration in the liver and kidneys. Chronic effects on these and other systems should be evaluated in appropriate long-term studies.

Environmental Effects: The environmental release of pyridine may pose a hazard to aquatic biota and terrestrial life. Residues have been detected in water and uptake in plants has been reported. Although a wide range of toxicity has been measured for plant and animal life in short-term bioassay tests, the results of one longer-term exposure to *Daphnia magna* indicates a potential for chronic toxicity. More testing is needed to determine the biological significance of residues and the potential effects of long-term exposures on both plant and animal life.

Epidemiology: Pyridine has been reported to have an effect on the central nervous system in humans, as well as to produce injury to the liver and kidney. Given the large number of workers exposed, epidemiological studies should be undertaken.

3.2.H 1,1,1-TRICHLOROETHANE

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Epidemiology

SUBSTANCE IDENTIFICATION: CAS NO. 71-55-6

REASON FOR RECOMMENDATIONS:

Production, Release, and Exposure: This compound is produced primarily for use as a cleaning solvent for metals and other materials. 1,1,1-Trichloroethane (methyl chloroform) has the potential to replace the chlorinated ethylenes in a variety of solvent formulations used commercially. The U.S. production of this compound totaled approximately 630 million pounds in 1976. Current release rates are not known; however, it is estimated that over 300 million pounds of this compound are employed in dispersive uses which would principally result in releases to the atmosphere. The significant adverse effects on the upper atmosphere have been evaluated. Minor amounts may also enter the aquatic and terrestrial environment. NIOSH estimates that about 3,000,000 persons may be exposed to this material in the workplace.

Carcinogenicity: The currently available information, including recent results from the NCI carcinogenesis bioassay program, indicates that data are not adequate to make a judgment on the carcinogenic potential of 1,1,1-trichloroethane. The Committee recommends that this chemical be evaluated with respect to carcinogenicity.

Mutagenicity: The absence of information on the mutagenicity of this compound indicates that such studies should be undertaken.

Teratogenicity: The Committee concludes that the current available information on teratogenic effects is insufficient to judge the hazard potential of this material. Consequently, it is recommended that appropriate teratogenesis studies be undertaken on 1,1,1-trichloroethane.

Other Chronic Effects: There is insufficient evidence regarding the impact of chronic, low-level exposure to 1,1,1-trichloroethane. Chronic effects, with specific attention to neurological, cardiovascular and renal systems, should be evaluated in appropriately designed studies.

Epidemiology: No investigations of health effects in occupational workers exposed to 1,1,1-trichloroethane were found during the Committee's review of this material. Given the large population of workers exposed to this compound, it is recommended that appropriate epidemiological investigations be conducted.

REFERENCES

1. Preliminary List of Chemical Substances for Further Evaluation, Toxic Substances Control Act Interagency Testing Committee, July 1977.

2. Initial Report to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, October 1, 1977. Published in the Federal Register, Vol. 42, No. 197, Wednesday, October 12, 1977, pp. 55026-55080. The report and the supporting dossiers also were published by the Environmental Protection Agency, EPA 560-10-78/001, January 1978.

3. Human Health and the Environment - Some Research Needs, A report of the Second Task Force for Research Planning in Environmental Health Sciences, DHEW Publication No. NIH 77-127, Chapter 16, 1977.

INFORMATION DOSSIERS ON SUBSTANCES
DESIGNATED BY
TSCA INTERAGENCY TESTING COMMITTEE

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FOREWORD

This document has been prepared for the Toxic Substances Control Act (TSCA) Interagency Testing Committee by its technical contractor, Clement Associates, Inc. The Committee is charged with making recommendations to the Administrator of the Environmental Protection Agency (EPA) with respect to which chemicals EPA should give priority for testing to determine adverse effects on man or the environment.

The dossiers in this document were originally drafted by Clement and were reviewed in detail by the Committee, which in certain instances added information. Conclusions made by Clement scientists about specific studies were also reviewed by the Committee. The information in the dossiers reflects the collective knowledge and judgment of the Committee and its technical contractor. These dossiers have been used by the Committee as the primary basis for recommending the chemicals for priority testing.

The dossiers were designed to provide the Committee with information on the chemicals' physical and chemical properties, exposure characteristics, and biological properties that was in sufficient detail to support an informed judgment on whether they should be given priority for testing.

The dossiers are not comprehensive critical reviews. They contain information from the National Library of Medicine's TOXLINE and the Environmental Mutagen Information Center (EMIC) automated data banks. Standard secondary sources (see Appendix A--General References), monographs, criteria documents, reviews, and reports available from government agency files and trade association libraries were also consulted. Material received in response to the Committee's request in the July 1977 Federal Register for information on certain substances was also reviewed. Clement scientists and Committee members also relied upon their own knowledge of the literature to supplement the data derived from these sources. Secondary sources and abstracts were consulted first in preparing the dossiers. When an article was judged to contain information of major significance or to require a critical review, the primary source was consulted. Except when indicated otherwise, the information cited in these dossiers was derived from the primary sources.

ACRYLAMIDE

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ACRYLAMIDE

AN OVERVIEW

Acrylamide occurs as colorless, odorless crystals and is stable at room temperature, but it may polymerize violently on melting. It is insoluble in benzene and heptane, soluble in alcohol, ether, and acetone, and very soluble in water and chloroform.

NIOSH reported that 70 million pounds of acrylamide were produced in the United States in 1974. According to an EPA report, 64 million pounds were produced in 1976. The compound has a wide range of uses, the major ones being as a crosslinking agent in polymer manufacture and in sewage and waste water treatment. It is also used in permanent press fabrics; in adhesives, paper, and textile sizes; in chemical grouting; and in soil conditioning agents. Small quantities are used for flocculation of ores and in synthesis of dyes.

According to the NIOSH criteria document, approximately 20,000 workers in the United States are potentially exposed to acrylamide.

Due to its high water solubility, the compound is likely to enter rivers and other waters if released into the environment. This may be significant in ground water and in deep bedrock aquifers where biodegradation is absent. However, in surface water it is expected to be hydrolyzed to acrylic acid and ammonia, to be biodegraded by microorganisms, or to react through its double bond with chlorine, bisulfite, or ammonia.

In experimental studies with acrylamide, rats excreted approximately 60% of an administered dose in the urine, either as metabolites or unchanged.

The neurotoxic effects of acrylamide are well known and have been extensively documented. In animal studies, incoordination, convulsions, behavioral and EEG changes, peripheral neuropathies, sensory loss, and paralysis have been reported. Signs of acrylamide poisoning in workers include polyneuritis, sensory loss, muscle weakness, absence of tendon reflexes, imbalance, numbness, and positive Romberg's sign. There have been two reports of negative results in the Ames test, and one report of no adverse effects in the offspring of pregnant rats exposed to acrylamide.

Acrylamide may pose major hazards to human and aquatic life as a result of several factors, including the leaching of residual monomer from polyacrylamides in soil grouts, in waste-treatment sludge and ore-tailing deposits, and in polyacrylamide flocculants used in clarifying and purifying waste waters.

ACRYLAMIDE

PART I

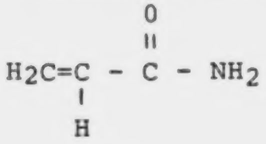
GENERAL INFORMATION

1.1 Identification CAS No.: 000079061
NIOSH No.: AS33250

1.2 Synonyms and Trade names

Acrylic amide; propenamide; propenoic acid amide (G16, G22)

1.3 Chemical Formula and Molecular Weight



$H_2C{=}\underset{\displaystyle H}{\underset{|}{C}} - \overset{\displaystyle O}{\overset{\|}{C}} - NH_2$

C_3H_5NO Mol. wt. 71.08 (G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless, odorless crystals; the solid is stable at room temperature but may polymerize violently on melting. (G21)

1.4.2 Boiling Point: 125°C (25 mm) (G21)

1.4.3 Melting Point: 84-85°C (G22)

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure: 1.6 mm at 84.5°C (G15)

1.4.6 Solubility: Insoluble in benzene, heptane; soluble in alcohol, ether, acetone; very soluble in water, chloroform (G21, G22)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production: 15-20 million lb (1966)
32 million lb (1972)
70 million lb (1974)
(1, as cited in 2)
64 million lb (1976) (3)

1.5.2 Use: As a cross-linking agent; in adhesives, paper and textile sizes, soil grouting and conditioning agents, and flocculants; in sewage and waste water treatment; in ore processing; in permanent press fabrics; in the synthesis of dyes, etc.; in secondary and tertiary oil recovery

(G21,3)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information was found in the sources searched.

1.6.2 NIOSH Estimates of Occupational Exposure:

NOHS Rank: 2987

Estimated no. of persons exposed: 7,000*

*rough estimate

(G29)

In its criteria document, NIOSH estimated that 20,000 workers are potentially exposed to acrylamide in the United States (2).

1.7 Manufacturers and Suppliers

American Cyanamid Co.
Cemco, Inc.
Conray Chemicals, Inc.
Eastman Kodak Co.
Polysciences, Inc.
Vistron Corp.

(G37)

ACRYLAMIDE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

No specific evidence for or against the bioaccumulation of acrylamide was found in the sources searched, and its octanol/water partition coefficient was not available. Although acrylamide is highly soluble in water (215.5 g/100 ml water at 30°C (G23)), it is also soluble in chloroform, and therefore probably has a potential for slight bioaccumulation.

2.2 Impurities and Environmental Degradation or Conversion Products

Acrylamide is available commercially in solid state (G17) and as a 50% aqueous solution by weight (3). As a solid, acrylamide is stable and requires no stabilizers, but in solution it is unstable and tends to polymerize. Polymerization inhibitors added to commercial solutions of the chemical are hydroquinone, tert-butyl pyrocatechol (G23), cupric and ferrous salts, N-phenyl-2-naphthylamine, cupferron, and tetramethylthiuram monosulfide (bis(dimethylthiocarbamoyl)sulfide) (G17). Ammonium and calcium sulfate, acrylic acid, sulfuric acid, acrylonitrile, beta-hydroxyproprionamide, and water are other possible contaminants, depending on the mode of synthesis (G17,3). One solid product in a "technical" grade is reported to be 97% pure (G21) and another in a "commercial" grade to be 98% pure (G17). Specifications for the commercial product allow 0.8% water, 0.0015% Fe, 0.02% water insolubles, and 1.5% butanol insolubles (G17). Specifications for a 50% aqueous solution were 50±2% water by weight, pH 5.2-6.0, a boiling point of 105.5°C, a specific gravity of 1.04, and a crystallization point of 12-13°C (3).

Ammonia, bisulfite, and chlorine (from water treatment), all present in the environment, are known to react with the double bond of the compound (3). The chlorination product, 2,3-dichloroproprionamide, is a vesicant (3). The ammonia and bisulfite adducts are reported to have potential uses as acrylamide scavengers (3).

Fatty acid amides are generally metabolized to the corresponding acid and amine (G38). Environmental degradation of acrylamide is expected to follow a similar course: it will probably hydrolyze to ammonia and acrylic acid, both of which may be toxic to fish and other organisms. Acrylamide is also readily biodegraded in several days by sewage, soil, and river microorganisms; the degradation products were not specified (3).

2.3 Acute Toxicity

The acute toxicity of acrylamide, as reported in the NIOSH Registry of Toxic Effects of Chemical Substances (G16), is given in Table I-1.

TABLE I-1
ACUTE TOXICITY OF ACRYLAMIDE

Parameter	Dose (mg/kg)	Species	Route
LD50	170	Rat	Oral
"	170	Mouse	"
"	170	"	i.p.
LDLo	126	Rabbit	Oral
"	1,000	"	Skin
"	252	Guinea pig	Oral

Paulet and Vidal (4) determined LD50 values of 124 and 90 mg/kg for acrylamide given to Wistar rats by the oral and intraperitoneal routes, respectively. Spencer and Schaumburg (5) reviewed the literature on the effects of acrylamide in animals, focusing on its neurotoxicity. Unpublished studies cited in this review have demonstrated a sequence of clinical findings in dogs, cats, mice, rats, rabbits, and frogs given 100-5,000 mg/kg of the chemical. Depending on the route of administration and the dose, neurologic and circulatory manifestations became apparent. Some animals died, and the suspected cause was respiratory failure. EEG changes were also seen in decerebellate, decerebrate, and decorticate cats exposed to acrylamide (23). A convulsive episode, with recovery within 24 hours, in a cat given a single treatment with 100 mg/kg was reported.

2.4 Other Toxic Effects

Spencer and Schaumburg (5) stated that the induction of neuropathies by exposure to acrylamide was the most consistent finding. In a review article, these authors mentioned the higher susceptibility of older animals and the absence of sex-specific reactions. Cats given 0.3-1 mg/kg and monkeys given 1-3 mg/kg daily for 1 year were stated to have shown no toxic symptoms. Doses of 10-50 mg/kg/day, by all routes, elicited peripheral neuropathy. Hind limb signs (not specified) were seen by 2 weeks in suckling rats given 50 mg/kg/day of acrylamide intraperitoneally for 6 days and in 40-100 days in baboons fed 10 mg/kg/day in fruit. Cats given 20 mg/kg/day showed adverse signs in 4-6 days, while those receiving 10 mg/kg/day showed none until the 13th-15th day.

Bradley and Asbury (27) reported that mice given acrylamide in their drinking water at 250 ppm for 45 days lost weight and hair and had difficulty in using their hind legs. After the treatment had ended, weight gain and improved gait were observed within five days. In animals autopsied on day 23 of the treatment, histopathological examination revealed degeneration of myelinated fibers.

To evaluate the safety of the commercial use of polymers or copolymers, which might contain small amounts of residual acrylamide, McCollister et al. (22) gave rats polymer samples containing 0.07-0.81% residual acrylamide. The authors mixed the polymer samples with rat feed to give acrylamide concentrations of 3, 9, 30, 70, 90, 110, 300, and 400 ppm. The rats were dosed for

90 days by dietary and intragastric feeding. In animals receiving acrylamide at 300 ppm, loss of the use of hindquarters and loss of proprioception were reported.

McCollister et al. (22) fed cats and monkeys acrylamide 5 days/week at 0.83-10 mg/kg for 1 year. The authors observed weakness and loss of control of the hindquarters in both species.

Hopkins (18) reported that the main features of clinical illness in seven baboons given acrylamide (injected into fruit as a 10% solution in water) at 10, 15, or 20 mg/kg/day for 29-192 days were weakness of the jaw and facial muscles, paralysis, and extensive damage to peripheral nerves.

Leswing and Ribelin (6) determined the effects of acrylamide on 11 cats and 4 Cebus monkeys. The animals were given the chemical orally at 20 mg/kg/day, but the daily dose for the monkey was increased to 30 mg/kg by about the 8th week. In 2-3 weeks, all of the cats showed clinical signs of hind limb weakness, unsteadiness of the posterior part of the body, and eventually paralysis. Anorexia, weight loss, rhinitis, and eye infection were also noted.

Monkeys were reported to have been less sensitive than cats to the chemical's toxicity (6). They received doses 50% larger before they showed similar adverse signs. Pathological examinations revealed abnormalities in the nerves of the caudal limbs. Degeneration of myelin and axons was more severe distally than proximally. The authors stated that all the animals showed marked clinical improvement several weeks after returning to an acrylamide-free diet but that conduction velocity was depressed.

Barnes (7) reported that doses of acrylamide given to young rats by mouth at 100 mg/kg/day for 2 days was lethal for most rats. When acrylamide was given at 400 ppm in the diet, signs of disability were apparent within 4 weeks, and the effects were more severe by 8 weeks. Full information on data was not provided.

Female rats given acrylamide at 50 mg/kg/day were reported to have shown alterations in ambulatory and rearing behavior, but those given 20 mg/kg/day did not (10). Rats given acrylamide for 9-22 days at 20, 30, and 50 mg/kg/day were said to have had depressed body weight increase, food intake, and fecal and urinary output.

Drees et al. (9) found no neurotoxicity in newborn rabbits given subcutaneous injections of acrylamide in 0.5 and 5 mg/kg doses daily for 12 weeks. In 17 of 23 rabbits given 50 mg/kg/day for 5 weeks, neurotoxic effects were first observed on the 24th day. When the rabbits were taken off the treatment for 7 weeks, all but one were said to have returned to normal. No changes were detected in hematological and biochemical tests or in gross and histopathological examinations.

Edwards (8) studied the neurotoxic effects of acrylamide in nine hens given 50 mg/kg of acrylamide orally, three times a week. Ataxia was observed in two hens after four doses, in five after six doses, and in the other two after nine doses. Four hens recovered 2-3 months after treatment was stopped. Histopathological alterations were seen in the peroneal and sciatic nerves from some of the hens with marked ataxia.

Edwards (8) reported that three doses in one week of acrylamide at 50 μg/g injected into the dorsal sac of five frogs was lethal in three and a 2-hour exposure to a 2% (w/v) solution killed two out of three frogs. Surviving frogs were said to have been free of toxic signs.

Sharma et al. (11) incubated in vitro cultures of nerve fibers, neuroglia, and neurons from dorsal chick ganglia with acrylamide at 37°C for 72 hours. Light and phase microscopic evaluation revealed that acrylamide at 2.1×10^{-4} and 3.8×10^{-4} M had a half-maximal inhibitory effect on the fibers and the neuroglia, respectively. The authors reported complete inhibition of cell growth at 10^{-2} M, whereas acrylamide at 10^{-5} M was noninhibitory.

Several studies have reported instances of toxicity in workers exposed to acrylamide. Six persons in two factories in England were reported to have had severe polyneuropathy, and it took 1 year for complete recovery from the symptoms (13). Kesson et al. (12) reported acrylamide poisoning in six construction workers. The patients were between 26 and 57 years old and were exposed to the chemical for 19-36 weeks. Signs and symptoms included sweating, peeling skin, abnormal skin sensations, sensory loss, muscle weakness, absence of tendon reflexes, and positive Romberg's sign. The less affected patients recovered, but little recovery occurred in two patients after 1 year.

Auld and Bedwell (14) reported the case of a New Brunswick miner who worked 35 hours/week loading hoppers with a 10% aqueous solution of acrylamide. The first symptoms, noted af-

TABLE I-2

SUMMARY OF EFFECTS OF ACRYLAMIDE EXPOSURE ON HUMANS

Number of Subjects	Duration and Route of Exposure	Observed Effects	References
6	3-24 mo, dermal and possible inhalation	Erythema, excessive sweating, muscular weakness	14-16 Brinkley*
8	3-13 mo, dermal and possible inhalation	Loss of weight, anorexia	13,15-17, 19
6	4-7 mo, dermal and possible inhalation	Eye irritation, skin rash, fatigue, confusion	14,17
7	2 mo-8 yr, dermal and possible inhalation	Gastrointestinal upset	20
5	1 mo, ingestion	Rhinorrhea, urinary and fecal retention, ecchymoses	21
9	7-12 mo, dermal and possible inhalation	Vertigo, abnormal reflexes, emotional changes	14,15, 17,19
4	3-24 mo, dermal and possible inhalation	Ataxia, hypoesthesia	14-16
17	1 mo-8 yr, dermal and possible inhalation	Pain, tremor, desquamation, sensory loss	13,14, 15,20
10	1-15 mo, dermal and possible inhalation	Positive Romberg's sign	13,15 17,19

*From D.R. Brinkley (written communication, June 1976)

Adapted from the NIOSH Criteria for a Recommended Standard--Occupational Exposure to Acrylamide(2)

TABLE I-3

SUMMARY OF EFFECTS OF ACRYLAMIDE EXPOSURE ON ANIMALS

Routes of exposure	Animal	Dose and Duration	Observed Effects	References
Dermal	Rabbit	0.5-1.0 g/kg, 24 hr	Edema, death 1/5	22
"	"	10% solution, 3 days	On abraded skin, slight reddening, edema	22
"	"	10% solution, 2 wk	On shaved skin, no effects	22
Ocular	"	10 and 40%, 24-48 hr	Pain, conjunctival irritation	23
Oral	Rat	203-277 mg/kg, 1 dose	LD50, death 5/5	22,24,25
"	"	50-126 mg/kg, 1-15 days	Lethargy, weakness, bladder distension	7
"	"	100 mg/kg, 2-3 days	Death of most animals	7,24,26
"	"	0.3-11 mg/kg, 55-189 days	No effects	22,24
"	"	200-400 ppm, 1-6 mo	Loss of motor control, ataxia, leg weakness, progressive paralysis	7,8,22,24,26
"	"	100 ppm, 6-40 wk	Growth retardation, leg weakness	22,24
"	"	10-50 ppm, 6 wk	No effects	26
"	Mouse	170 mg/kg, 1 dose	LD50	26
"	"	250 ppm, 45 days	Weight loss, ataxic gait	27

TABLE I-3 (continued)

Routes of Exposure	Animal	Dose and Duration	Observed Effects	References
Oral	Rabbit	252 mg/kg, 1 dose	Death 4/4	22
"	"	126 mg/kg, 1 dose	Death 1/4; tremors, pupil dilation	22
"	Guinea pig	252 mg/kg, 1 dose	Death 4/4	22
"	"	126 mg/kg, 1 dose	No deaths, slight weight loss	22
"	Cat	1-20 mg/kg, 53-367 days	Weakness, paralysis, twitching	6
"	"	0.03-0.3 mg/kg, 367 days	No effects	22
"	Dog	5-100 mg/kg, 4-5 wk	Ataxia, sedation, weakness	20,26
"	"	1-8 mg/kg, 4-19 wk	No effects	26
"	Monkey	10-30 mg/kg, 8-10 wk	Weakness, decreased nerve conduction velocity, myelin and axonal degeneration	6,22
"	"	0.03-3 mg/kg, 51 wk	No effects	22
i.p.	Rat	50-100 mg/kg, 4-6 wk	Weight loss, paralysis, bladder distension, myelin and axonal destruction	28,29
"	Monkey	100 mg/kg, 2 days	Lung and kidney congestion, liver necrosis, severe weakness, death	22
i.v.	"	50 mg/kg, 4 days	Death within 4 days	22
s.c.	Cat	10 mg/kg, 21-61 days	Ataxia, absent Achilles tendon jerks, interruption of nerve function	30

TABLE I-3 (continued)

Routes of Exposure	Animal	Dose and Duration	Observed Effects	References
Oral, i.p., i.v., i.m., s.c.	Cat	1-50 mg/kg (duration not specified)	Ataxia, progressive weakness, gradual blood-pressure drop to shock level; death of some animals	17

Adapted from the NIOSH Criteria for a Recommended Standard--Occupational Exposure to Acrylamide (2) ter 7 weeks, included dermatitis, weakness in the legs and hands, and poor balance. Later signs were blueness, coldness, and profuse sweating of the extremities, numbness, and tenderness. At the time the worker was hospitalized, his bluish-red forearms, hands, lower legs, and feet dripped perspiration and were cold to touch. Temperature and vibration sensations were slightly impaired, tendon reflexes were absent, and the patient showed general weakness and unsteadiness. The man's condition had returned to normal 14 weeks after he was removed from exposure to acrylamide.

The effects of acrylamide exposure on humans and animals are summarized in Tables I-2 and I-3, which were adapted from the NIOSH criteria document on acrylamide (2).

The ACGIH Threshold Limit Value (TLV) for acrylamide is 0.3 mg/m^3, with a "skin" notation (G11), and NIOSH has recommended a limit of 0.3 mg/m^3, as a TWA, for occupational exposure to the substance (2). The OSHA limit for skin exposure is 300 μg/m^3 (G16).

2.5 Carcinogenicity

No information was found in the sources searched.

2.6 Mutagenicity

Acrylamide was reported to have given negative results in Ames assays run independently by NIOSH (31) and American Cyanamid (36). In the NIOSH study, bacteria were exposed to 25-500 μl of acrylamide in DMSO (1 μg/μl DMSO), in the presence and absence of rat liver homogenate (0-50 µl of S-9 fraction/plate) (31). No evidence of mutagenicity was apparent in the Salmonella tester strains TA 98, TA 100, TA 1535, and TA 1537. American Cyanamid tested acrylamide at 1,000 µg in Salmonella typhimurium strains TA 98, TA 100, TA 1530, TA 1535, and TA 1538 without rat liver homogenate.

2.7 Teratogenicity

Edwards (32) evaluated the teratogenic effects of acrylamide by giving it to pregnant rats either in the diet at levels of 200 and 400 ppm from the day of mating until parturition or by single intravenous injections at 100 mg/kg (in water) on day 9 of gestation, which according to the author is when the nervous system is most susceptible to teratogenic effects. No macroscopic skeletal or organ abnormalities were observed in the offspring, even at doses that produced neuropathy in the mothers. However, it is possible that acrylamide in utero causes reversible damage to fetal nerves.

2.8 Metabolic Information

The metabolic fate of acrylamide was extensively reviewed by Spencer and Schaumburg (5) and in a NIOSH criteria document (2).

Spencer and Schaumburg (5) cited two unpublished studies in which ^{14}C-labeled acrylamide became widely distributed in the body and showed the highest affinity for vascular organs (doses, exposure, and species not specified). In another study cited by Spencer and Schaumburg, tadpoles totally immersed in a solution of labeled acrylamide showed distribution in the brain, nerves, and other unspecified organs. Ando and Hashimoto (37, as reported in 5) reported that, in mice given labeled acrylamide by injection, 2.5 times more radioactivity was detected in the distal half of the sciatic nerve than in the proximal part and 4 times more radioactivity was found in the distal half of the sciatic nerve than in the brain. This finding was considered significant because of the reported damage to the distal peripheral nerve.

Hashimoto and Aldridge (28) injected two male rats intravenously with a single ^{14}C-labeled dose of acrylamide at 100 mg/kg. About 6% of the dose was exhaled as carbon dioxide in the first 8 hours, followed by very slow excretion afterward. Forty percent of the dose was excreted in urine within the 1st day and more than 60% by day 3. The urinary metabolites were not identified. On the 1st, 4th, and 14th day after treatment, ^{14}C was detected in whole blood, plasma, brain, spinal cord, sciatic nerve, liver and kidney, with the highest activity in the blood. The large amount of activity present on the 14th day was presumed to be protein-bound.

Data noted by Spencer and Schaumburg (5) indicated that in rats 40-65% was excreted in 24 hours and 60-85% in 3-4 days. From 80-89% of the urinary label was thought to be in metabolites, but some investigators have maintained that acrylamide is excreted unchanged.

The half-life of acrylamide in the blood of rats given 100 mg/kg intravenously was reported to be 1.9 hours (33, as reported in 2).

It has also been suggested that acrylamide might be metabolized in the liver, because rats pretreated with either phenobarbitol or DDT showed 100% failure in rotarod performance (a measure of neurological deficit) only after they were given 520 and 600 mg/kg of acrylamide, respectively, in a single intraperitoneal injection, while rats that were not pretreated showed 100% failure when given a 360 mg/kg dose (34, as reported in 2).

2.9 Environmental Release and Ecological Effects

Acrylamide may enter the environment from a number of sources. It is released at manufacturing sites, at polymer-application sites as residual monomer, and in transportation and handling. High environmental concentrations of acrylamide may result from its use in chemical grouting, for example in the sealing of sewage collection systems to prevent groundwater infiltration and in soil stabilization at construction sites. In soil grouting, residual acrylamide monomer may come in direct contact with surface or ground waters. It could potentially travel great distances in ground water or aquifers where biodegradation is reported to be absent. Leaching of residual monomer from polyacrylamide in waste-treatment sludge and ore-tailing deposits as well as run-off and seepage from irrigation sites where acrylamide-containing waste water is used are other sources of contamination. Polyacrylamide flocculants are widely used in clarifying and purifying industrial and municipal waste waters. Monomeric residues from these flocculants may contaminate the environment (3).

One ecological incident has been described (3). A road in Japan 2.5 meters from a well was chemically grouted--a process that involves incomplete in situ polymerization. All members of a family of five who used the well became ill, exhibiting a number of neurological signs. They recovered after they stopped using the well, which was found to contain acrylamide at 400 ppm.

Edwards (8) reported that seven goldfish exposed to acrylamide at 100 ppm died in 5-7 days, but that exposure at 50 ppm for 30 days caused no toxic effects. Paulet and Vidal (4) reported a 72-hour LC50 of 140 ppm for goldfish. Edwards (8) reported that exposure to acrylamide was fatal to frogs (see Section 2.4, Other Toxic Effects).

2.10 Current Testing

Tox-Tips (35) reported that the Environmental Protection Agency (J.P. Lewkowski et al., Health Effects Research Laboratory, Cincinnati, Ohio) is conducting pathological examinations on Sprague-Dawley rats. The animals were exposed to unspecified doses of acrylamide in drinking water for 14 weeks in a behavioral toxicity study. An identical experiment is planned in which tissues from exposed animals will be examined for neurophysiological effects.

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ARYL PHOSPHATES

AN OVERVIEW

Four different aryl phosphate compounds are included in this dossier: cresyl diphenyl phosphate, triphenyl phosphate, trisisopropylphenyl phosphate, and tritolyl phosphate. A number of other aryl phosphates, including some containing alkyl as well as aryl ester linkages, are also manufactured. Aryl phosphates are either liquids or solids that are generally soluble in organic solvents but insoluble in water.

Six different manufacturers of the aryl phosphates discussed in this dossier have been identified in the United States. No data are available on the manufacturers or the production volume of trisisopropylphenyl phosphate; the latest available production figures for the other three compounds reviewed in this dossier range from 4.5 to 51 million pounds per year.

Aryl phosphates are used as components of high pressure lubricants and hydraulic fluids and as plasticizers, gasoline additives, and flame retardants. EPA regulations aimed at preventing damage to automotive catalysts allow only trace concentrations of phosphorus in additives in unleaded gasoline. As a result, the use of aryl phosphates as gasoline additives will decline as unleaded gas assumes a larger share of the market.

Occupational exposure estimates by NIOSH range from less than 1,000 workers for trisisopropylphenyl phosphate to more than 2,000,000 for tritolyl phosphate.

Data on the bioaccumulation of aryl phosphates are limited. Because of the aryl phosphates' high stability and their low solubility in water compared to their solubility in organic solvents, some biostorage is likely. Uptake and storage of aryl phosphates by fish and other aquatic food-chain organisms have been reported.

Certain aryl phosphates are known to produce degenerative damage to the peripheral (motor) nervous system, which results in flaccid paralysis. One of these, tri-ortho-tolyl phosphate, is highly toxic and has been implicated in numerous incidents of human poisoning that have resulted in varying degrees of paralysis. Subchronic feeding studies with triphenyl phosphate have been reported, but long-term carcinogenicity studies are lacking. No information was found on the mutagenicity or teratogenicity of the aryl phosphates.

Commercial triaryl phosphate mixtures have been reported to produce toxic effects in rainbow trout after prolonged exposure. Several aryl phosphates have been found to potentiate the effects of organophosphate pesticides on insects, and tri-ortho-tolyl phosphate has been shown to produce such potentiation in other organisms, including mammals.

ARYL PHOSPHATES

PART I

GENERAL INFORMATION

CRESYL DIPHENYL PHOSPHATE

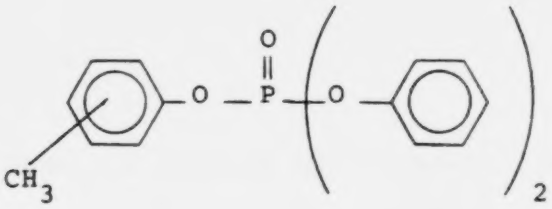
1.1 Identification CAS No.: 026444495
NIOSH No.:

1.2 Synonyms and Trade Names

CDP; cresylphenyl phosphate; phosphoric acid, cresyl diphenyl ester; Phosflex 122; Santicizer 140; Kronitex MX; Kronitex K-3

(1,31,G21)

1.3 Chemical Formula and Molecular Weight



Mol. wt. 340.32

$C_{19}H_{17}PO_4$

1.4 Chemical and Physical Properties

1.4.1 Description: Probably appears seldom as a pure compound; usually as a mixture of ortho-, meta-, and para-cresyl diphenyl phosphates; clear transparent liquid; very slight color

(G21)

1.4.2 Boiling Point: 390°C (1)

1.4.3 Melting Point: -38°C (1)

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure: 0.08 mm at 200°C (1)

1.4.6 Solubility: Insoluble in water; soluble in most organic solvents except glycerol

(G21)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production:

Production:	14.6 million lb (1972)	(G28)
	14.1 million lb (1973)	(1)
	7-8 million lb (1975)	(G41)
	4.5 million lb (1976)	(G24)

1.5.2 Use:

As a plasticizer; as an extreme pressure lubricant; in hydraulic fluids; in food packaging; as a gasoline additive

(G21)

Use of phosphorus-containing additives in unleaded gasoline is limited by the EPA to trace quantities (0.005 g phosphorus/gal, maximum); use of aryl phosphate as additives should decline as use of unleaded gasoline increases.

(2)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information was found in the sources searched.

1.6.2 NOHS Occupational Exposure:

Rank: 1176

Estimated no. of persons exposed: 89,000*

*rough estimate

(G29)

1.7 Manufacturers

IMC Chem. Group
Stauffer Chemical Co.
Monsanto Industrial Chemicals Co.
Sobin Chemicals Co.
FMC Corp.

(1,G31)

TRIPHENYL PHOSPHATE

1.1 Identification

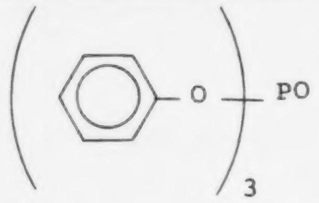
CAS No.: 000115866
NIOSH No.: TC84000

1.2 Synonyms and Trade Names

Celluflex TPP; phosphoric acid, triphenyl ester; TPP; Phosflex TPP

(1,G16)

1.3 Chemical Formula and Molecular Weight



$C_{18}H_{15}PO_4$

Mol. wt. 326.29

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless, odorless, crystalline powder (G21)

1.4.2 Boiling Point: 370°C (1)

1.4.3 Melting Point: 49.2°C (1)

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure:

No information was found in the sources searched.

1.4.6 Solubility: Insoluble in water; soluble in alcohol and chloroform; very soluble in ether, benzene, and carbon tetrachloride (G22)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production: 10.6 million lb (1970) (G28)

1.5.2 Use: At present, used exclusively as a plasticizer, primarily with cellulosics such as cellulose acetate and cellulose nitrate, but also in newer rigid thermosetting materials, such as polyphenylene oxide, and in synthetic rubbers

(1)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information was found in the sources searched.

1.6.2 NOHS Occupational Exposure:

Rank: 1154

Estimated no. of persons exposed: 95,000*

*rough estimate

(G29)

1.7 Manufacturers

Eastman Kodak
Monsanto Industrial Chemicals Co.

(G24)

TRISISOPROPYLPHENYL PHOSPHATE

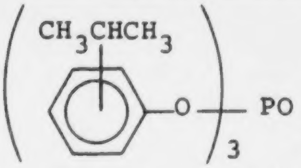
1.1 Identification

CAS No.:
NIOSH No.:

1.2 Synonyms and Trade Names

No information found in sources searched

1.3 Chemical Formula and Molecular Weight



$C_{27}H_{33}PO_4$ Mol. wt. 452.53

1.4 Chemical and Physical Properties

1.4.1 Description: Probably a mixture of phenyl and isopropylphenyl ester isomers; liquid (G25)

1.4.2 Boiling Point: 250°C at 4 mm (G25)

1.4.3 Melting Point: <-25°C (G25)

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure:

No information was found in the sources searched.

1.4.6 Solubility:

No information was found in the sources searched.

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production:

No information was found in the sources searched.

1.5.2 Use: In late 1970, FMC Corp. introduced trisisopropylphenyl phosphate as a substitute for tritolyl phosphate (see uses for tritolyl phosphate)

(G25)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information was found in the sources searched.

1.6.2 NOHS Occupational Exposure:

Rank: 5167

Estimate no. of persons exposed: <1,000*

*rough estimate

(G29)

1.7 Manufacturers

FMC Corp.

(G25)

TRITOLYL PHOSPHATE

1.1 Identification

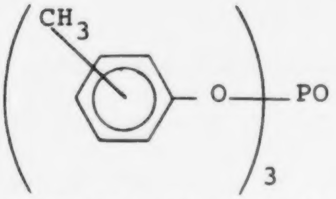
CAS No.: 001330785
NIOSH No.: TD01750

1.2 Synonyms and Trade Names

Phosphoric acid, tris(methylphenyl) ester; tricresyl phosphate; TCP; PX-917; Celluflex; Kronitex; Lindol

(G23)

1.3 Chemical Formula and Molecular Weight



$C_{21}H_{21}PO_4$ Mol. wt. 368.36

(G23)

1.4 Chemical and Physical Properties

1.4.1 Description: A mixture of isomeric tritolyl phosphates, usually excluding the very toxic ortho isomer as much as possible; oily, flame-resistant liquid

(G23)

1.4.2 Boiling Point: 420°C (G21)

1.4.3 Melting Point: -20°C ("congealing point") (G25)

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure:

No information was found in the sources searched.

1.4.6 Solubility: Insoluble in water (<0.002% at 85°C); soluble in all proportions in common organic solvents and thinners, linseed oil, china wood oil, castor oil

(G23)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production:

50.2	million lb (1972)	(G28)
50.6	million lb (1973)	(G25)
56	million lb (1974)	(G28)
51	million lb (1975)	(G41)

1.5.2 Use:

As a plasticizer in vinyl plastics manufacturing; as a flame retardant; as a solvent for nitrocellulose; in cellulosic molding composition; as an additive to extreme pressure lubricants; as a nonflammable fluid in hydraulic systems; as a lead scavenger in gasoline; to sterilize certain surgical instruments

(G23)

Use of phosphorus-containing additives in unleaded gasoline is limited by the EPA to trace quantities (0.005 g phosphorus/gal, maximum); use of aryl phosphates as additives should decline as use of unleaded gasoline increases

(2)

Quantitative Distribution:	Percentage
Functional fluids and lubricants	55
Plasticizers, flame retardants	30
Air filter adhesive mediums	5
Gasoline additive, automotive chemicals	2
Miscellaneous	8
	100

(G25)

Consumer Product Information:

Category	No. of products containing tritolyl phosphate	No. of tritolyl phosphate products in category / Total no. of products in category x 100
Paints, varnishes, shellac, rust preventatives, etc.	22	0.2%
Flame-retardant chemicals	9	1.5%
Household aerosols	1	0.03%
Adhesives and adhesive products including glue	1	0.19%

The 33 products surveyed contained an average of 8.3% tritolyl phosphate.

(G27)

1.6 Exposure Estimates

1.6.1 Release Rate: 43.4 million lb

(G28)

1.6.2 NOHS Occupational Exposure:

Rank: 32

Estimated no. of persons exposed: 2,282,000*

(G29)

*rough estimate

1.7 Manufacturers

FMC Corp.
Monsanto Co.
Sobin Chemicals, Inc.
Stauffer Chemical Co.
IMC Chemical Group, Inc.

(G24,G25)

TABLE II-I

CHARACTERISTICS OF ARYL PHOSPHATES

Name	Solubility	Log P_{oct}	Estimated Environmental Release (million lb)	Production (million lb)	Estimated No. of Persons Exposed (Occupational)	Use
Cresyl diphenyl phosphate	i in H_2O; s in most os	*	*	14.6 (1972) 14.1 (1973) 7-8 (1975) 4.5 (1976)	~89,000	Plasticizer, lubricant gasoline additive, in food packaging
Triphenyl phosphate	i in H_2O; s in alc, chl; vs in eth, bz, and CCl_4	*	*	10.6 (1970)	~95,000	Plasticizer
Trisiso-propyl-phenyl phosphate	*	*	*	*	<1,000	See Tritolyl phosphate
Tritolyl phosphate	i in H_2O; ∞ in oos, linseed oil, china wood oil, castor oil	*	43.5	50.2 (1972) 50.6 (1973) 56 (1974) 51 (1975)	~2,300,000	Plasticizer, flame-retardant, solvent, additive to lubricants and hydraulic fluids, lead scavenger in gasoline

*No information was found in the sources searched.

Key to Abbreviations:

i -- insoluble
s -- soluble
os -- organic solvents
alc -- alcohol
chl -- chloroform

vs -- very soluble
eth -- ether
bz -- benzene
∞ -- soluble in all proportions
oos -- ordinary organic solvents

ARYL PHOSPHATES

PART II

BIOLOGICAL PROPERTIES

ARYL PHOSPHATE GROUP

2.1 Bioaccumulation

Few data were found on the bioaccumulation of the particular aryl phosphates discussed in this dossier. Some aryl phosphates are likely to biostore because they are highly stable and are less soluble in water than in organic solvents. One study provided indirect evidence of the uptake of a commercial aryl phosphate mixture from water by trout. Hydrolysis of muscle tissue from fish exposed for 4 months to IMOL S-140 aryl phosphate at 0.9 mg/liter in a flow-through system yielded cresols not detected before hydrolysis. These cresols were not detected before or after hydrolysis of tissue from unexposed fish (3). Preliminary findings in another study indicated that aryl phosphates were taken up by fish in their natural environment (4). In model ecosystem studies, tri-p-cresol phosphate has been found to accumulate and persist in all the aquatic test organisms used (30).

2.2 Impurities and Environmental Degradation or Conversion Products

Aryl phosphate products are generally mixtures. For example, some tricresyl phosphate, dicresyl phenyl phosphate, and triphenyl phosphate can be expected in cresyl diphenyl phosphate. The cresyl (same as tolyl) moiety in tricresyl phosphate is a mixture of ortho, meta, and para isomers. The relative amount of each isomer depends on the nature of the cresol raw material (G25). The concentration of the ortho-tolyl moiety is deliberately kept low during synthesis to favor synthesis of the meta and para isomers and thus avoid formation of the highly toxic ortho-tolyl phosphates (7). In air, triphenyl and tritolyl phosphates react with hydroxyl radical with an estimated half-life of 4 days (G14). In water, hydrolysis is moderately rapid at pH 10 (half-life 30 days) and extremely slow at pH 7 (half-life many years) (G14). Phosphates generally hydrolyze with loss of ester groups to give phosphoric acid, the corresponding phenols, and their degradation products, e.g., quinones. Hydrolysis of the diester is usually the slowest step (4). One report indicated that an aryl phosphate was metabolized by a soil microorganism (G14).

2.3 Acute Toxicity

See Section 2.3 for each aryl phosphate.

2.4 Other Toxic Effects

In man and other species, certain aryl phosphates may produce damage to central or peripheral nerves, leading to paralysis. Aryl phosphates may also produce inhibition of cholinesterases in erythrocytes and plasma. The tris(alkylphenyl) phosphates specifically depress intestinal and hepatic phenylbutyrate esterases (G10). Several aryl phosphates, such as tri-ortho-tolyl phosphate, have been found to produce delayed neurotoxic effects (8).

Accidental poisoning of cattle was reportedly caused by triaryl phosphates (TAP's) escaping from a gas pipeline compressor station. The clinical signs were posterior motor paralysis, dyspnea, diarrhea, and agalactia (absence or failure of milk secretion). This incident prompted a study in which cattle were given oral doses of TAP at 0.5-1 g/kg. The cattle exhibited axonal degeneration of the spinal cord and cholinesterase depression (9, from TOXLINE abstract).

The relationship between the delayed neurotoxicity of aryl phosphates and their chemical structures has been reviewed (8). The neurotoxic aryl phosphates include those with one or more ortho-alkyl-substituted aryl groups having at least one hydrogen on the alpha carbon. Para-alkyl-substituted aryl phosphates can also be neurotoxic if the alpha carbon of the substituent has at least two hydrogen atoms.

Tri-ortho-tolyl phosphate has caused severe human poisoning. (See 2.4 for tritolyl phosphate.)

A NIOSH criteria document on organophosphates is to be submitted to the Department of Labor in 1980 (G16).

2.5 Carcinogenicity

No tumors were reported in two short studies with animals exposed to triphenyl phosphate. See Triphenyl Phosphate, Section 2.5. No additional information on the carcinogenicity of the aryl phosphates discussed in this dossier was found in the sources searched.

2.6 Mutagenicity

No information was found in the sources searched.

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

The results of a metabolism study of tri-ortho-tolyl phosphate have been reported (see Tritolyl Phosphate, Section 2.8), but no metabolic information was found on the other aryl phosphates discussed in this dossier.

2.9 Environmental Release and Ecological Effects

A synthetic triaryl phosphate lubricating oil (IMOL S-140) was reported not to be acutely toxic to rainbow trout; the fish, however, slowly developed signs of poisoning during prolonged exposure. They refused food, their fatty tissues became discolored, and SGOT and LDH activities increased (3). At concentrations as low as 0.25 mg/liter, a triaryl phosphate hydraulic fluid (Pydraul 50E) was reported to produce toxic effects in rainbow trout (27). These observations suggest that triaryl phosphates could have long-term effects on ecological systems. Several aryl phosphates have been found to potentiate the effects of organophosphate pesticides on insects (28, as reported in 4). Tri-ortho-tolyl phosphate has been shown to produce such potentiation in other organisms, including mammals (29).

(See also Tritolyl Phosphate, Section 2.9.)

2.10 Current Testing

See Section 2.10 for each aryl phosphate.

CRESYL DIPHENYL PHOSPHATE

2.1 Bioaccumulation

See Aryl Phosphate Group, Section 2.1.

2.2 Impurities and Environmental Degradation or Conversion Products

See Aryl Phosphate Group, Section 2.2.

2.3 Acute Toxicity

Reported oral LD50 values for cresyl diphenyl phosphate are 6.4-12.8 g/kg for rats and mice and 1.6-3.2 g/kg for guinea pigs (G38). No paralysis occurred at these doses, although there was some dyspnea at the higher doses. In guinea pigs, neither skin irritation nor absorption through skin was observed.

The Stauffer Chemical Company (10) reported that the oral LD50 for cresyl diphenyl phosphate was >4,640 mg/kg in rats. The dermal LD50 in rabbits also was reported to be >4,640 mg/kg. In rabbits, the substance was nonirritating in a 4-hour dermal exposure, and a single dose caused no eye irritation.

2.4 Other Toxic Effects

See Aryl Phosphates Group, Section 2.4.

2.5 Carcinogenicity

No information was found in the sources searched.

2.6 Mutagenicity

No information was found in the sources searched.

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

No information was found in the sources searched.

2.9 Environmental Release and Ecological Effects

See Aryl Phosphate Group, Section 2.9.

2.10 Current Testing

Stauffer Chemical Company plans to conduct neurotoxicity tests on cresyl diphenyl phosphate (10).

TRIPHENYL PHOSPHATE (TPP)

2.1 Bioaccumulation

See Aryl Phosphate Group, Section 2.1

2.2 Impurities and Environmental Degradation or Conversion Products

See Aryl Phosphate Group, Section 2.2

2.3 Acute Toxicity

The acute toxicity of triphenyl phosphate (TPP), as reported in the NIOSH Registry of Toxic Effects of Chemical Substances (G16) and by Sutton et al. (11), is given in Table II-2.

TABLE II-2

ACUTE TOXICITY OF TRIPHENYL PHOSPHATE

Parameter	Dosage	Animal	Route
LDLo	3,000 mg/kg	Rat	Oral
LD50	6.1 g/kg	"	"
"	2.0 g/kg	Cat	"
"	100 mg/kg	"	Subcutaneous
"	0.1-0.2 g/kg	Chicken	"

TPP has low acute toxicity for rats, mice, and guinea pigs (11). In cats, it produced delayed generalized illness paralysis. It was slowly absorbed when administered orally o injected in alcohol solution, and it was poorly absorbed through the skin and produced no dermal irritation. Although TPP inhibited cholinesterase in vitro and in vivo, it was not a potent anticholinesterase agent in rats, mice, guinea pigs, and cats (11).

Hine et al. (7) reported that TPP administered subcutaneously at 0.5 g/kg and orally at 1.0 g/kg failed to produce paralytic effects in white leghorn cockerels. There was no evidence of degeneration in the brain, spinal cord, or sciatic nerve. TPP given orally at 2 g/kg caused severe depression of plasma cholinesterases 24 hours after administration. Studies with fowl plasma in vitro showed no anticholinesterase activity for TPP.

Triphenyl phosphate (dosage unspecified) apparently produced erythrocyte cholinesterase inactivation (G10).

Acute toxicity data from the literature on TPP are summarized in Table II-3. (See also Table II-2.)

2.4 Other Toxic Effects

A secondary source (G26) reported that triphenyl phosphate was more neurotoxic than tritolyl phosphate in cats but probably not in humans. TPP was said to have caused a delayed but peripheral neuritis involving motor neurons, which resulted in a flaccid paralysis, particularly of the distal muscles. No sensory disturbances were observed. Signs of cholinesterase inhibition also were detected. A later review (8), however, reported that pure TPP was not neurotoxic in the hen and the cat and suggested that other aryl phosphates present as impurities might have been responsible for earlier observations of neurotoxicity.

TABLE II-2

SUMMARY OF ACUTE TOXICITY DATA ON TRIPHENYL PHOSPHATE (11)

Route	Animal	Dose	Effect	Reference Cited
Oral	Fowl (unspecified)	25 g/kg (total)	No death or paralysis in 2/2	12
"	"	0.5-2 g/kg	No death or paralysis in 4/4	13
"	"	1.0 g/kg	No paralysis in 4/4	7
Inhalation	Mouse	757 mg/m^3 for 2 hr	Significantly reduced cholinesterase activity	11
Dermal	"	0.5 ml (70% in ethanol) for 24-72 hr	Absorption but no irritation	11
Subcutaneous	Monkey	1.0 g/kg	Rapid paralysis	14
"	"	0.5 g/kg	Paralysis	14
"	Cat	0.3-1 g/kg	Death in 4/4	13
"	"	0.2 g/kg	Paralysis and death in 3/3	13
"	"	0.1 g/kg	No paralysis in 2/2	13
"	Fowl (unspecified)	0.5 g/kg	No paralysis in 4/4	7
Intraperitoneal	Cat	0.1-0.4 g/kg	Paralysis in 2/6 in 16-18 days, followed by anorexia, weakness, weight loss, exaggerated deep tendon reflex	13
	[illegible]	[illegible]	Death in 1/6, no paralysis	13

TPP at 10^{-2} M showed no neurotoxic effects on sympathetic ganglia from chick embryos (15).

Rats fed 0.5% TPP for 35 days showed a slightly depressed growth rate. No hematological or gross pathological changes were observed, although the liver weights were significantly increased (11). These effects were not observed in rats fed 0.1% TPP for 35 days (11).

TPP administered orally to rats and mice at one-tenth to one-half of the LD50 for 3 months had no significant toxic effects, nor were there any irritating effects on rat skin (16, from TOXLINE abstract).

One person developed dermatitis after dermal exposure to carbon paper containing TPP (17, from TOXLINE abstract).

The 1976 ACGIH Threshold Limit Value (TLV) for triphenyl phosphates was 3 mg/m^3 (G11).

2.5 Carcinogenicity

Hierholzer et al. (18, as reported in G18) observed no tumors in 12 rats fed TPP at 1 g/kg for 90 days. The same investigators also obtained negative results for carcinogenicity in shorter feeding studies with cats and rats. Sutton et al. (11) detected no tumors in cats given TPP by single intraperitoneal injections at up to 0.4 g/kg or in rats fed 0.5% TPP in their diet for 35 days.

2.6 Mutagenicity

No information was found in the sources searched.

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

No information was found in the sources searched.

2.9 Environmental Release and Ecological Effects

See Aryl Phosphate Group, Section 2.9.

2.10 Current Testing

No information was found in the sources searched.

TRISISOPROPYLPHENYL PHOSPHATE

2.1 Bioaccumulation

See Aryl Phosphate Group, Section 2.1.

2.2 Impurities and Environmental Degradation or Converstion Products

See Aryl Phosphate Group, Section 2.1.

2.3 Acute Toxicity

No data were found on the acute toxicity of trisisopropylphenyl phosphate. However, the toxic effects of isopropylphenyl diphenyl phosphate have been studied by Stauffer Chemical Company, which reported that the substance was nonirritating (10) and had low toxicity. The LD50 of the substance is greater than 2,000 mg/kg in rabbits given a single dose by either the dermal or oral route (10). Rabbits exposed dermally for 4 hours showed no irritation, and a single dose caused no eye irritation (10).

2.4 Other Toxic Effects

See Aryl Phosphate Group, Section 2.4.

2.5 Carcinogenicity

No information was found in the sources searched.

2.6 Mutagenicity

No information was found in the sources searched.

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

No information was found in the sources searched.

2.9 Environmental Release and Ecological Effects

See Aryl Phosphate Group, Section 2.9.

2.10 Current Testing

No information was found in the sources searched.

TRITOLYL PHOSPHATE

2.1 Bioaccumulation

See Aryl Phosphate Group, Section 2.1.

2.2 Impurities and Environmental Degradation or Conversion Products

See Aryl Phosphate Group, Section 2.2.

2.3 Acute Toxicity

The acute toxicity of tritolyl phosphate, as reported in the NIOSH Registry of Toxic Effects of Chemical Substances (G16), is given in Table II-4.

TABLE II-4

ACUTE TOXICITY OF TRITOLYL PHOSPHATE

Parameter	Dosage	Animal	Route
LDLo	4,680 mg/kg	Rat	Oral
"	500 mg/kg	Dog	"
"	100 mg/kg	Rabbit	"

The Stauffer Chemical Company (10) evaluated the acute toxicity of this compound (isomer unspecified). The oral LD50 in rats and the dermal LD50 in rabbits were stated to be greater than 4,640 mg/kg. In rabbits, the substance was non-irritating in a 4-hour dermal exposure, and a single dose caused no eye irritation. The LC50 for a 1-hour inhalation exposure was greater than 8.6 mg/liter in rats.

Cells from the spinal cords of chickens given 0.5 ml of tritolyl phosphate in a single dose showed cytoplasmic fibrillization, mitochondrial degeneration, and a variety of large osmiophilic masses in the cell body and processes (19). Neither the isomer used nor the route of exposure was specified.

Dollahite and Pierce (20) administered Cellulube 220, a mixture of triphenyl phosphate, tritolyl phosphate (isomer unspecified), trixylenyl phosphate, and trialkylphenyl phosphate, by stomach tube to rats, rabbits, chickens, goats, and calves in single doses of 2-60 g/kg. Calves, goats, and rabbits were apparently most susceptible, chickens were less affected, and rats showed no signs of toxicity. The data are summarized in Table II-5. The signs of toxicity included dyspnea, tympanites, lack of coordination, and paralysis, and some animals died. Red blood cell cholinesterase levels were reported to have decreased in calves, goats, and rabbits but not in chickens.

TABLE II-5

REPORTED SINGLE DOSE ORAL TOXICITY OF CELLULUBE 220 (20)

Animal	Dosage	Observations
Rat	10-20 g/kg	No toxic effects
Rabbit	2 g/kg	Healthy
"	5 g/kg	Signs of illness in 1/5, 1 death
"	6 g/kg	Anorexia, salivation, diarrhea, trembling, and paralysis
Chicken	20 g/kg	No toxic effects

TABLE II-5 (continued)

Animal	Dosage	Observations
Chicken	20-40 g/kg	Paralysis in 3/11
"	60 g/kg	No toxic effects
Goat	5 g/kg 10 g/kg	Anorexia, incoordination, dyspnea, and paralysis in 19-36 days
Calf	7.7 g/kg	Signs on the 19th day similar to those in goats, death on the 30th day

2.4 Other Toxic Effects

Brown et al. (G14) summarized the chronic toxicity of tritolyl phosphate (isomer unspecified) in studies with experimental animals as follows: "Repeated dose effects include gastrointestinal disturbances, ataxia, paralysis, adrenal hypertrophy, cretinuria (sic), nerve degeneration, and EEG alternations. Effects reported in the rat, cat, guinea pig, rabbit and unspecified primate."

Saito et al. (21, from TOXLINE abstract) reported that oral administration of tritolyl phosphate (isomer unspecified) at 30-1,000 mg/kg/day to rats for 3 months produced no deaths and no signs of toxicity except temporary salivation. However, serum albumin levels were significantly decreased in male and female rats, and the level of serum urea nitrogen was increased in females. Females had increased relative liver weights. Hypertrophy of the zona fasticulata in the adrenal gland of some rats was also noted.

Degenerative changes seen in spinal ganglion mitochondria of prosimians poisoned with tritolyl phosphate (isomer unspecified) indicated mitochondrial involvement in TTP poisoning (22, from TOXLINE abstract).

The ortho isomer (tri-ortho-tolyl phosphate or tri-ortho-cresyl phosphate) has been implicated in many cases of human poisoning. Sax (G4) summarized epidemiological data on these incidents, as follows:

> Most of the cases of tri-o-cresyl phosphate poisoning have followed its ingestion. In 1930, some 15,000 persons were affected in the United States, and of these, 10 died. The responsible material was found to be an alcoholic drink known as Jamaican ginger, or "jake." This beverage had been adulterated with about 2% of tri-o-cresyl phosphate. The affected persons developed a polyneuritis, which progressed, in many cases, with degeneration of the peripheral motor nerves, the anterior horn cells and the pyramidal tracts. Sensory changes were absent. Since 1930 there have been several other outbreaks of poisoning following ingestion of the material. Recently 3 cases of polyneuritis occurring in England in connection with the manufacture of the tri-o-cresyl phosphate have been reported. Absorption was probably through the respiratory tract, though there may have been some absorption through the skin. All three men made a good recovery.
>
> From ingestion experiments with cockerels, it appears that tri-o-cresyl phosphate is more toxic than the m form, and much more so than tri-p-cresyl phosphate or triphenyl phosphate.
>
> Irrespective of whether absorption has been by ingestion or by inhalation or skin absorption, the history is usually one of early, transient gastrointestinal upset, with nausea, vomiting, diarrhea and abdominal pain. These clear up, and are followed in 1 to 3 weeks by soreness of the lower leg muscles, "numbness" of the toes and fingers, and a few days later by weakness of the toes and bilateral foot-drop. After another week or so, weakness of the fingers and bilateral wrist-drop follow. There are no sensory changes. Recovery is slow, and the degree of residual paralysis depends upon the extent of damage to the nervous system. Many cases recover completely. In 1958 several thousand persons in Morocco were poisoned

with this material which was present in lubricating oil which had been mixed with edible oils by dishonest merchants. Many of the victims suffered a permanent paralysis.

Liver biopsies from six patients affected with polyneuritis after exposure to tri-ortho-tolyl phosphate showed changes in hepatocytes, which were characterized by vacuolar swelling of the cytoplasm with abnormalities of the nuclear membrane and lipofuscin pigment accumulation (23, from TOXLINE abstract).

The 1976 ACGIH Threshold Limit Value (TLV) for tri-ortho-tolyl phosphate was 0.1 mg/m^3 (G11).

2.5 Carcinogenicity

No information was found in the sources searched.

2.6 Mutagenicity

No information was found in the sources searched.

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

To determine the metabolic fate of tri-ortho-tolyl phosphate, Sharma and Watanabe (5,6) administered an oral dose (0.77 g/kg) of the substance to chickens. They found that 26.5% of the dose was excreted in 72 hours. The metabolites were not fully characterized, but at least one was considered to be hydroxylated on the phenyl ring in at least one position. Almost all (99%) of the chemical excreted during the first 72 hours of the experiment was unchanged material.

2.9 Environmental Release and Ecological Effects

Tritolyl phosphate (isomer unspecified) was moderately toxic to fish, with an Aquatic Toxicity Rating (96-hr TLm, species unspecified) of 10-1 ppm (G16). Stauffer Chemical Company (10) reported that tritolyl phosphate had an LD50 greater than 1,000 ppm and less than 5,000 ppm in sticklebacks exposed for 96 hours.

Tri-ortho-tolyl phosphate inhibited esterases in houseflies, mosquitoes, and lepidopteran larvae, slowing the metabolism of insect growth regulators and phthalate esters (24, 25, from TOXLINE abstract). It has been reported to have potentiated the effects of organophosphate pesticides on other organisms, including mammals (29).

Tritolyl phosphate (isomer unspecified) is reportedly used at a concentration of 2% in a fish-net preservative that is of low toxicity to fish but prevents fouling by other marine organisms. The other components of the preservative are methyl isobutyl ketone (81%), copper oleate (5%), polyvinyl chloride (5%), beta-pyrene (5%), and tributyl tin oxide (2%) (26, from TOXLINE abstract). (See also Aryl Phosphate Group, Section 2.9.)

2.10 Current Testing

No information was found in the sources searched.

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CHLORINATED NAPHTHALENES

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CHLORINATED NAPHTHALENES

AN OVERVIEW

Chlorinated naphthalenes are oily liquids or waxy solids, insoluble in water but soluble in most organic solvents. The commercial products are mixtures of chloronaphthalenes and are defined by their chlorine content and approximate melting point.

Halochem, Inc., reported to be the only manufacturer of chlorinated naphthalenes in the world, produces mixtures containing monochloro, dichloro, trichloro, and tetrachloro derivatives for a world market of 700,000 pounds a year. Overall production has declined in recent years; production of the pentachloro through octachloro derivatives has been discontinued recently.

These products are used in the manufacture of capacitors, as engine oil additives, in electroplating, and in fabric dyeing. According to the NOHS, approximately 5,000 persons are occupationally exposed to them in the United States.

Data on occupational toxicity and cattle poisoning incidents in the 1940's and 1950's suggest that chlorinated naphthalenes are hazardous pollutants. While the physical and chemical properties of the chlorinated naphthalenes suggest that they have a high potential for bioaccumulation, this has not been verified experimentally. The high thermal stability of chlorinated naphthalenes and their resistance to chemical attack indicate that they will persist in the environment, with their persistence increasing as chlorine content becomes greater. No reports of their effects were found, and the extent of their distribution in the environment is not known. Few data are available on their toxicity to fish and wildlife.

Chlorinated naphthalenes are strong irritants. As their chlorination increases from monochloronaphthalene to hexachloronaphthalene, their toxicity generally increases as well. Few data are available on the toxicity of the heptachloro and octachloro derivatives. The most common toxic effects in humans, generally as a result of occupational exposure, are chloracne and liver damage. No information on the carcinogenicity, mutagenicity, and teratogenicity of the compounds was found in the sources searched.

CHLORINATED NAPHTHALENES

PART I

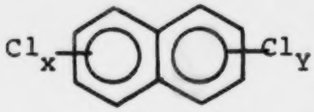
GENERAL INFORMATION

1.1 Identification (see Section 1.8, Table III-1)

1.2 Synonyms and Trade Names

Chloronaphthalene, oil; chloronaphthalene, wax; N-oil; N-wax; Halowax (production discontinued) (G21,1)

1.3 Chemical Formula and Molecular Weight



$C_{10}H_{8-(x+y)}Cl_{x+y}$ Mol. wt. 162.62 to 403.74

(G22)

(x + y = 1 through 8)

1.4 Chemical and Physical Properties

1.4.1 **Description:** The technical grade monochloronaphthalenes and dichloronaphthalenes are liquids at room temperature; the higher chlorinated compounds are solids. Industrial chlorinated naphthalenes are liquid or solid mixtures of chloronaphthalenes defined by their chlorine contents, approximate melting points, and often also by their color.

The oils are almost colorless, thin mobile liquids and are combustible. The waxes are varied in color.

Chloronaphthalene crudes, darker in color than the refined products, are also commercially available. They may contain impurities such as chlorinated biphenyls, fluorenes, pyrenes, anthracenes, and dibenzofurans.

(G17,G21,2)

1.4.2 **Boiling Point:** (see Section 1.8, Table III-2)

1.4.3 **Melting Point:** (see Section 1.8, Table III-2)

1.4.4 **Solubility:** Insoluble in water; soluble in practically all organic solvent liquids and oils (wax must be heated)

(G21,G22)

1.5 Production and Use

1.5.1 Production: <5 million lb (1972)
Declined slightly from 1972-1974 (1)

The current total world market is reported to be 700,000 lb/yr (3)

1.5.2 Use: In the manufacture of electronics materials (capacitors) and as an engine oil additive; less commonly in electroplating and fabric dyeing

1.6 Exposure Estimates

1.6.1 NOHS Occupational Exposure:

Rank: 3439

Estimated no. of persons exposed to chlorinated naphthalenes: 5,000*

*rough estimate (G29)

(see also Section 1.8, Table III-1)

1.7 Manufacturers

Halochem, Inc. (now the only manufacturer; trade name: N-Oil and N-Wax) (3)

Koppers Company (formerly a producer; trade name: Halowax)

1.8 Data on Specific Chlorinated Naphthalenes

TABLE III-I

IDENTIFICATION AND EXPOSURE DATA FOR MAJOR CONSTITUENTS OF CHLORINATED NAPHTHALENE MIXTURES

			NOHS Occupational Exposure	
Name	NIOSH No.	CAS No.	Rank	No. of Persons Exposed*
1-Chloronaphthalene	QJ21000	000090131	3760	3,000
Dichloronaphthalene	-	028699889**	6443	150
Trichloronaphthalene	QK40250	001321659**	5056	1,700
Tetrachloronaphthalene	QK37000	001335882**	5458	1,000
Pentachloronaphthalene	QK03000	001321648**	-	-
Hexachloronaphthalene	QJ73500	001335871**	-	-
Octachloronaphthalene	QK02500	002234131**	-	-

*Rough estimate
**Generic CAS number (assigned when isomer is not specified)

TABLE III-2

CHARACTERISTICS OF COMMERCIALLY AVAILABLE CHLORONAPHTHALENE MIXTURES (1,2)

Halochem Inc. Product	Koppers Co. Product*	Derivatives Present (approx. percentage)	Chlorine Content	Boiling Point	Melting Point	Uses
Monochloronaphthalene	Halowax 1031	95% mono 5% di	22%	250°C	-25°C	Engine oil additive; proprietary uses in fabric
N-Oil 12	Halowax 1000	70% mono 30% di	26%	250°C	-33°C	"
N-Wax 34 (and 34S)	Halowax 1001 (and 1001S)	7% di 30% tri 63% tetra	50%	308°C	93°C	Impregnating automobile capacitors
N-Wax 43 (and 43B)	Halowax 1099 (and 1099B)	2% di 15% tri 83% tetra	52%	315°C	102°C	"
N-Wax 45**	Halowax 1013	10% tri 50% tetra 40% penta	56%	328°C	120°C	Electroplating stopoff compounds; impregnating carbon electrodes used in chlorine production
N-Wax 56** (and 56B)	Halowax 1014	20% tetra 40% penta 40% hexa	62%	344°C	137°C	"
N-Wax 80**	Halowax 1051	10% hepta 90% octa	70%	370°C	185°C	Unknown

*Chlorinated naphthalenes no longer produced by Koppers Co.

**No longer produced (3)

CHLORINATED NAPHTHALENES

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Based on their low water solubility, low volatility, and resistance to degradation, the chlorinated naphthalenes have a high potential for storage and persistence in living matter (4). As their chlorine content increases, their chemical and thermal stability increase while their water solubility decreases, thereby raising their potential for bioaccumulation. The reported presence of traces of chlorinated naphthalenes in dead birds in the Netherlands (5) also indicates a potential for bioaccumulation. The highest accumulation factor for algae exposed to chlorinated naphthalenes for 24 hours, however, was 140, a figure that is considered low for algae (6).

Green and Neff (7) studied the effects of three Halowax chlorinated naphthalenes on grass shrimp (Palaemonetes pugio). After the aquatic LC50's had been determined, the shrimp were exposed to the test compound at 40 ppb for up to 15 days. Most of the bioaccumulation occurred in the first 3 days. The levels of accumulated chlorinated naphthalenes were greatly reduced after the shrimp were exposed to clean sea water for 5 days. The bioconcentration factor and LC50's for the three substances are given in Table III-3.

TABLE III-3

ACUTE TOXICITY AND BIOCONCENTRATION OF THREE CHLORINATED NAPHTHALENES (7)

Substance	Approximate Composition	96-hr LC50	Bioconcentration Factor
Halowax 1000	60% mono 40% di	325 ppb	63
Halowax 1013	10% tri 50% tetra 40% penta	-	187
Halowax 1099	40% tri 60% tetra	90 ppb	257

2.2 Impurities and Environmental Degradation or Conversion Products

Possible impurities in chlorinated naphthalenes are chlorinated derivatives of biphenyl, fluorene, pyrene, anthracene, and dibenzofuran (G17). Vos and Beems (8) have reported that commercial chlorinated naphthalenes were contaminated with chlorinated dibenzofurans and that at least some of the toxic effects (chloracne and liver damage) might be attributable to the contaminants. Chlorinated naphthalenes have been found in PCB's produced in foreign countries (2). In PCB's manufactured in the United States, they were found at lower levels (9, as reported in 2).

Chlorinated naphthalenes have high thermal stability, are stable to oxidizing agents, and are resistant to chemical attack at ordinary temperatures (G17). Their low vapor pressure limits their entry into the atmosphere by direct volatilization. Because the photolysis of polychlorinated naphthalenes in methanol at 300 nm caused carbon-chlorine bond fission and dimerization, Ruzo et al. (10) concluded that environmental degradation of chloroaromatics may be more efficient through photochemical pathways than through metabolic routes, although exposure of 1,5-dichloronaphthalene and 2-chloronaphthalene as a solid film to sunlight irradiations led to an insoluble polymeric material.

Environmental decomposition of chlorinated naphthalenes has received little attention. Microbial degradation studies of the monochlorinated naphthalenes have shown that these compounds are degraded by bacteria in soil and sewage sludge (11, 12 from abstract, 13). Biodegradation of chlorinated naphthalenes in the rabbit has been reported by Cornish and Block (14) and is described in Section 2.8. The monochloro and dichloro compounds are metabolized to hydroxy derivatives. The tetrachloro compounds are much less extensively metabolized, and those with five or more chlorines are metabolized at a rate too low to be detected, indicating that they are stored or poorly absorbed. Persistence in the environment, therefore, appears to increase as the degree of chlorination increases.

Two thirds of the reported (2) production of chlorinated naphthalenes is in the form of less chlorinated naphthalenes for use in temporarily closed systems (automobile capacitors). Pollution from this source depends on the extent of leaching from the capacitors when disposed of in sanitary landfills.

2.3 Acute Toxicity

Chlorinated naphthalenes are strong irritants. They may cause death or permanent injury after very brief exposures to small quantities (G4). A single oral dose of 1 g octachloronaphthalene was fatal to rabbits in 7 days (14). Chloracne has been experimentally induced in humans by applications of Halowax 1014, pentachloronaphthalene, and hexachloronaphthalene (15, as reported in 16).

2.4 Other Toxic Effects

Outbreaks of hyperkeratosis (X disease) in cattle in the 1940's and 1950's in the United States and Germany, according to a review by Crow (18), were the result of the accidental ingestion of chlorinated naphthalenes in wood preservatives and lubricating oils.

Hansel et al. (41) induced hyperkeratosis in calves by feeding them a wood preservative containing chlorinated naphthalenes. The authors did not describe the dosage regimen but reported that doses of 7-11 ml were fatal to 300-pound calves. Lacrimation, depression, and emaciation were observed in 3-6 weeks, and severe vitamin A deficiency occurred. From 30 ml of the preservative, fractionation procedures isolated 0.5 g of what the authors described as active material probably containing trichloronaphthalene and more highly chlorinated naphthalenes. A calf wearing a blanket that contained an unspecified amount of the same preservative developed severe lesions after 3 weeks.

Bell (42) gave one calf an oral dose of pentachloronaphthalene (as a 3% solution in vegetable oil) at approximately 22.0 mg/kg, a second calf an oral dose of hexachloronaphthalene (as a 3% solution in vegetable oil) at approximately 11.0 mg/kg, and a third calf an oral dose of unspecified chlorinated naphthalenes (as a 3% content of a lubricant) at 17.6 mg/kg. The doses were administered in gelatin capsules. Lacrimation, excessive salivation, and nasal discharge were observed in all three calves 3 days after treatment. The calf exposed to hexachloronaphthalene died on day 14 and the calf exposed to the unspecified chlorinated naphthalenes died on day 46. The calf exposed to pentachloronaphthalene was killed on day 57. Autopsies revealed hyperkeratosis, enlarged kidneys, bile duct proliferation and fibrosis of the liver, papillary proliferations of the oral mucosa, and squamous metaplasia of the epididymis. Link (43), reviewing the literature on bovine hyperkeratosis, described similar lesions as common signs of the disease; in addition, he listed squamous metaplasia of the seminal vesicles, Gartner's ducts, and salivary glands; mucoid papillary proliferation in the gall bladder; thickening of the gall bladder; and fibrosis in the pancreas.

Sikes et al. (19) reported that a 2-month-old calf nursing from a cow given octachloronaphthalene orally in capsules at approximately 12 mg/kg for 18 days developed hyperkeratosis. The authors concluded that either octachloronaphthalene or a toxic metabolite was excreted in milk.

Brock et al. (44) reported that the lowest concentration of chlorinated naphthalene (Halowax 1014) fatal to sheep was approximately 116 mg/kg. (The sheep were fed for an average of 106 days). This concentration was more than 100 times greater than the lowest fatal concentration for cows, which was reported as approximately 1 mg/kg, given for one week (the route of administration and the chlorine content of the chlorinated naphthalene were not specified) (45, as reported in 44). Affected animals showed nasal discharge, weakness, and weight loss. Pathological changes were apparently due to toxic effects on the cardiovascular system, the liver, and the kidneys. Myocardial damage, liver necrosis and cirrhosis, and degeneration of the nephrons were reported. Cardiac insufficiency and increased resistance to the flow of blood through the liver resulted in congestion of the spleen, kidneys, intestinal tract, and lungs.

Hyperkeratosis has been produced by oral administration of hexachloronaphthalene to rats and hamsters. In rats, mild to moderate fatty degeneration with centrilobular vacuolation of the hepatic cells was observed. Kidneys exhibited degenerative changes and necrosis of the tubules (17).

Pigs given hexachloronaphthalene orally at 22 mg/kg for 8-9 days exhibited depression, anorexia, and ataxia, but they did not develop other signs characteristic of bovine hyperkeratosis. Also observed were degenerative changes of the liver and kidneys, subacute interstitial duodenitis, and hyperplasia of the stratified squamous epithelium of the vaginal tissue accompanied by the formation of keratin on the mucosal surface (17).

The addition of 0.05 to 0.30% of octachloronaphthalene to the diet of rats accelerated the loss of vitamin A from the liver (20). Pentachloronaphthalenes and hexachloronaphthalenes fed to chickens led to chick-edema disease (21, as reported in 16). Chlorinated naphthalenes interfere with the biotransformation of carotene to vitamin A, an effect that is reported to be highly variable and subject to species-specific variation. Goats, sheep, swine, mice, chickens, and rats are much less susceptible than cattle (2).

Schwartz et al. (22, as reported in 16) indicated that in humans the most potent chloracne-producing agents were the chlorinated naphthalenes, chlorodiphenyls, and chlorodiphenyl oxides. Persons who worked with chlorinated naphthalenes usually developed acne after a month or more of exposure.

Chronic exposure to chlorinated naphthalenes generally produces both dermatological and systemic effects in humans. Among the former are acneform eruptions with pustules, papules, and large comedones; vesiculo-erythematous eruptions; simple erythematous eruptions with pruritis; and the appearance of dermatological lesions characterized by cysts that developed because the orifices of the sebaceous glands had been plugged (23).

Mixtures both of monochloronaphthalenes and dichloronaphthalenes and of trichloronaphthalenes and tetrachloronaphthalenes at 500 mg/g in a mineral oil suspension applied to the ears of humans led to no response during a 30-day period. A mixture of pentachloronaphthalene and hexachloronaphthalene caused acne, but heptachloronaphthalene and octachloronaphthalene, applied under the same conditions, did not (24, as reported in 2). Pentachloronaphthalene and hexachloronaphthalene at 30 mg/g in acetone (25, as reported in 2) also caused acne in humans.

Chlorinated naphthalenes have been reported to produce chloracne and, less frequently, systematic effects. These include jaundice produced by either an acute or subacute necrosis of the liver, acute hepatitis, anorexia, nausea, vomiting, or abdominal pain (23). Death after exposure to chlorinated naphthalene fumes has also been reported (26, 27). The liver is usually the only organ showing damage (25). Kleinfeld et al. (23), in a description of an incident in which workers were exposed to a mixture of tetrachloronaphthalene and pentachloronaphthalene, could make no definitive pronouncement on whether hepatic injury occurred.

Cotter (28, as reported in 16) reported seven cases of pentachloronaphthalene poisoning in workers engaged in the manufacture of insulated cable. Four of the workers developed jaundice and two died. Microscopic examination of the livers of the dead men showed complete loss of cells in some areas. Also the centrilobular areas were hemorrhagic, and prominent bile duct proliferation was observed in the periphery.

Toxic effects depend on the degree of chlorination. A summary of toxicity data on individual chloronaphthalenes and mixtures from a recent EPA report (2) are given in Table III-4.

The following Threshold Limit Values (TLV's) for skin exposure have been set for certain chlorinated naphthalenes (G11):

Trichloronaphthalene--5 mg/m^3
Tetrachloronaphthalene--2 mg/m^3
Pentachloronaphthalene--0.05 mg/m^3
Hexachloronaphthalene--0.2 mg/m^3
Octachloronaphthalene--0.1 mg/m^3

TABLE III-4

TOXICITY OF CHLORONAPHTHALENES (2)

Compound	Animal	Exposure and Route	Response	Reference Cited
Monochloronaphthalene	Rabbit	90 mg/g in acetone, applied to ear for 5-7 days	Mild reddening	24
"	"	590 mg/g in acetone, applied to ear	Severe reddening	25
Mixture of monochloronaphthalene and dichloronaphthalene	Human	500 mg/g in mineral oil suspension, applied to ear for 30 days	No effect	25
Dichloronaphthalene	Rabbit	45 mg/g and 290 mg/g in acetone	Reddening	25
"	Rat	5 g/kg, fed for 15 days	Increase in liver weight; growth impaired; coat texture roughened	29
Trichloronaphthalene	Mouse	2.5 mg/day, fed for 20 days	No dermatitis**	30
Mixture of trichloronaphthalene and tetrachloronaphthalene	Human	500 mg/kg in solvent, applied to ear for 30 days	No effect	24

TABLE III-4 (continued)

Compound	Animal	Exposure and Route	Response	Reference Cited
Mixture of trichloronaphthalene and tetrachloronaphthalene	Rat	3 g*, fed for 9-136 days	Fatty accumulation in liver cells	31
"	Rabbit	15 mg/kg/day fed for 60 days	No effect	32
"	Rat	1.31 mg/m^3, by inhalation for 16 hrs/day for 134 days	No effect	31
"	"	10.97 mg/m^3, by inhalation for 16 hrs/day for 102 days	Slight liver discoloration, swollen cells with slightly increased granularity and vacuolization of the cytoplasm**	31
Mixture of tetrachloronaphthalene and pentachloronaphthalene	"	500 mg/kg/day*, fed for 63 days	Fatal intoxication; jaundice and fatty degeneration of the liver	31
"	Rabbit	15 mg/kg/day, injected subcutaneously for 12-26 days	Fatal intoxication	32

TABLE III-4 (continued)

Compound	Animal	Exposure and Route	Response	Reference Cited
Pentachloronaphthalene	Pig	6% solution in lightweight lubricating oil, sprayed daily 6 days/week for 4 weeks (total approximate treatment volume: 3,000 ml of oil)*	Slight hyperkeratosis	33
Pentachloronaphthalene	Pig**	Total oral doses over 8-10 days:		
		50 mg/lb**	No vitamin A depression**	33 **
		70 mg/lb**	Marked vitamin A depression**	
		90 mg/lb**	3/3 deaths**	
Pentachloronaphthalene	Guinea pig (one animal)	2.5 mg/kg/day, orally 6 days/wk** for 48 days	Fatal	34
Mixtures of pentachloronaphthalene and hexachloronaphthalene	Human**	50% solution in mineral oil applied to skin at various locations for 35 days**	Acne**	24 **

TABLE III-4 (continued)

Compound	Animal	Exposure and Route	Response	Reference Cited
Mixtures of penta-chloronaphthalene and hexachloronaphthalene	Rat	300 mg/day, orally for 33 days or less (maximum dose of 9.9 g) or 100 mg/day, orally for 55 days (total dose of 5.5 g)	Fatal; livers markedly yellow with fatty degeneration	31
"	Poult	100 ppm in diet	16/18 deaths	21
"	"	5 ppm in diet	Some deaths; decrease in weight gain by 1/3	21
"	Rat	8.88 mg/m^3*, by inhalation 16 hr/day for 52 days	Jaundice; enlarged, yellow liver; fatal to 69%	31
"	Rabbit	15 mg/kg, orally for 12-26 days (total dose: 180-390 mg/kg)	Death; liver damage	32
"	"	30 mg/kg in acetone, applied to skin daily for 5 days	Mild dermatitis with follicular attentuation	25
Hexachloronaphthalene	Rat	20 and 63 mg/kg, in diet for 84 days	Weight loss	35
"	"	200 mg/kg, in diet	Some deaths	35

TABLE III-4 (continued)

Compound	Animal	Exposure and Route	Response	Reference Cited
Hexachloronaphthalene	Rabbit	30 mg/kg in acetone, applied to ear for 5 days	Decrease in sebaceous gland tissue	25
Heptachloronaphthalene				
No chronic studies reported in EPA Report (2)				
Octachloronaphthalene	Human	Applied to ear	No effects	24
"	Rat	0.5, 2, or 5 g/kg, in diet for 22 days	Decrease in vitamin A in liver but not in plasma	20
"	Rabbit	1 g, single oral dose	Death in 7 days	14
"	Poult	-	No effect	36

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*Corrected to agree with reference cited

**Added from reference

2.5 Carcinogenicity

No information was found in the sources searched.

2.6 Mutagenicity

No information was found in the sources searched.

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

Cornish and Block (14) investigated the metabolism of 1 doses of chlorinated naphthalenes in rabbits. They reported t 1-chloronaphthalene and dichloronaphthalene were metabolized readily and that tetrachloronaphthalene was metabolized to a somewhat lesser extent over a 4-day period. Pentachloronaphthalene, heptachloronaphthalene, and octachloronaphthalene did not undergo metabolic reactions that could be detected in this particular study.

Highly chlorinated naphthalenes were found to be excreted in the milk of cows suffering from X-disease (see Section 2.4) (19). In rabbits, the major excretory product was a glucuronide; small amounts of mercapturic acid derivatives, sulfates, and phenolic compounds were also excreted. For data on urinary metabolites in rabbits, see Table III-5. An inverse correlation existed between the extent to which chlorinated naphthalenes (from monochloro through pentachloro) were metabolized and excreted and the known toxicity of these compounds (14).

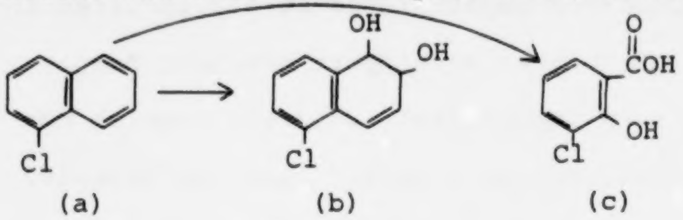
TABLE III-5

NAPHTHALENE AND LESS CHLORINATED NAPHTHALENES* ACCOUNTED FOR IN URINARY METABOLITES IN RABBITS (14)

	Compound Accounted for in Various Metabolites					
Compound Fed (1 g)	Ethereal Sulfate (mg)	Mercapuric Acid (mg)	Glucuronic Acid (mg)	Free Phenolic Compounds (mg)	Total Compound Excreted	Percentage of Compound Excreted
Naphthalene	64	192	390	23	669	67%
1-Chloronaphthalene	101	131	537	20	789	79%
Dichloronaphthalene	55	177	686	-	918	92%
Tetrachloronaphthalene	40	32	379	-	451	45%

*No pentachloronaphthalene, heptachloronaphthalene, or octachloronaphthalene fed to the rabbits could be accounted for in any of the four metabolites.

1-Chloronaphthalene, when metabolized by certain soil bacteria, may give D-6-chloro-1,2-dihydro-1,2-dihydroxynaphthalene and 3-chlorosalicylic acid, as diagrammed below (10):



(a) 1-Chloronaphthalene
(b) D-6-Chloro-1,2-dihydro-1,2-dihydroxynaphthalene
(c) 3-Chlorosalicylic acid

2.9 Environmental Release and Ecological Effects

Except for monochloronaphthalenes, few reports on the toxicity of chlorinated naphthalenes to aquatic and terrestrial wildlife were found in the sources searched, and none were found on their ecological effects. Little is known about the distribution of chlorinated naphthalenes in the environment. Goerlitz and Law (27) have noted that chlorinated naphthalenes, particularly those with three to six chlorine atoms, interfere in analyses of environmental samples for chlorinated pesticides and PCB's and that therefore they may be mistaken for them. The most reliable technique for analysis is gas chromatography/mass spectrometry. The detection of chlorinated naphthalenes in routine analyses for chlorinated hydrocarbons is unlikely unless they are specifically sought (2). The FDA, in monitoring agricultural products, can determine chlorinated naphthalene residues, but none were found from 1970-1975 (2). Chlorinated naphthalenes have been detected in the ppb range in fish in Lake Ontario (46).

Crump-Wiesner et al. (37, as reported in 2) found water samples containing chlorinated naphthalenes at 5.7 µg/liter in a South Florida drainage ditch near an airport overhaul hangar (their source may have been capacitors); sediment samples contained chlorinated naphthalenes at 5 mg/kg. Law and Goerlitz (38, as reported in 2) found chlorinated naphthalenes in the µg/kg range in material from the bed of the Guadalupe River in California, although there appeared to be no industrial activity in the vicinity.

From the foregoing, it appears that chlorinated naphthalenes have generally not been identified in the environment; it is not known, however, whether they are in fact absent or whether analytical capabilities for detecting them are unavailable.

Goldfish were rapidly intoxicated when exposed to chloronaphthalene at less than 1 ppm in water (39). The frog (*Rana pipiens*) had an LD50 of 900 mg/kg for 1-chloronaphthalene injected intraperitoneally in solution with peanut oil (39). Halowax 1000 (60% monochloronaphthalene and 40% dichloronaphthalene) had a 96-hour LC50 of 325 ppb in adult grass shrimp (*Palaemonetes pugio*). The LC50 for Halowax 1099 (40% trichloronaphthalene and 60% tetrachloronaphthalene) was 90 ppb (7). Chlorinated naphthalene mixtures were tested on four species of unicellular marine algae at concentrations from 0.1-1.0 ppm (6). Judged by the growth of the algae, toxicity appeared to be inversely proportional to the degree of chlorine substitution--an effect that is the reverse of what can be expected in mammals--while uptake was directly related to chlorine content. The 1- and 2-chloronaphthalenes were found to be very toxic to eggs of the sea urchin (Paracentrotus lividus) (40).

2.10 Current Testing

No information was found in the sources searched.

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DICHLOROMETHANE

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DICHLOROMETHANE

AN OVERVIEW

Dichloromethane, also known as methylene chloride, is a colorless, volatile liquid with a penetrating, ether-like odor. It is slightly soluble in water and soluble in all proportions in alcohol and ether.

Production of dichloromethane has steadily increased to an excess of 500 million pounds in 1976. Demand for the chemical is expected to increase as it substitutes for other compounds coming under regulation.

The compound is most commonly used as a paint remover. Other uses are as a propellant for aerosol sprays, a blowing agent in foams, and a degreasing agent.

NOHS reports that nearly 2,500,000 workers are exposed to dichloromethane in their places of employment.

An estimated 367 million pounds of dichloromethane are released annually into the environment. The chemical is nontoxic to sewage microorganisms and its Aquatic Toxicity Rating is in the nontoxic range. No reports of adverse ecological effects have been found, although some concern has been expressed about possible inhibition of natural fermentation processes.

In animals, acute exposure to dichloromethane has produced adverse effects on the heart and lungs; long-term exposure has produced toxic effects on the liver, lungs, eyes, and brain, as well as death. In humans, acidosis, hemoglobinuria, unconsciousness, elevated carboxyhemoglobin levels, increased pulse rate, paresthesia, sensations of heat, eye irritation, and nausea have been reported after acute exposure to the chemical. Long-term effects include sonorous breathing, cyanosis, rapid weak pulse, and biochemical changes in serum.

Metabolism of dichloromethane is thought to occur by enzymatic activation of the microsomal heme-oxygenase system. Carbon monoxide and carbon dioxide have been identified as metabolites. When inhaled or administered intraperitoneally, the chemical is largely eliminated unchanged in the breath.

No information on the carcinogenicity or mutagenicity of the chemical was found. One source reported an increased incidence of extra or split sternebrae in the offspring of mice exposed to it.

The chemical is being tested for its toxicity, carcinogenicity, and tissue-binding characteristics.

DICHLOROMETHANE

PART I

GENERAL INFORMATION

1.1 Identification

CAS No.: 000075092
NIOSH No.: PA80500

1.2 Synonyms and Trade Names

Methane dichloride; methylene bichloride; methylene chloride; methylene dichloride; Solaesthin

(G16)

1.3 Chemical Formula and Molecular Weight

CH_2Cl_2 Mol. wt. 84.93

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless, volatile liquid; penetrating ether-like odor (G23,G21)

1.4.2 Boiling Point: 40°C (G22)

1.4.3 Melting Point: $-95.1°C$ (G22)

1.4.4 Absorption Spectrometry:

λ_{max}^{vapor} <200 nm

(G22)

1.4.5 Vapor Pressure: 400 mm at 24.1°C (G22)

1.4.6 Solubility: Slightly soluble in water; soluble in all proportions in alcohol, ether (G22)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 **Production**: 471.3 million lb (1972) (G28)
537.7 million lb (1976) (G24)

1.5.2 **Use**: As a solvent for cellulose acetate; in degreasing and cleaning fluids; in paint removers; as a propellant for aerosol sprays; in plastics processing; as a blowing agent in foams; food extraction applications

(G23,G21,45)

Quantitative Distribution:

	Percentage
Paint remover	40
Exports	20
Aerosol sprays	17
Chemical specialties (mainly solvent degreasing)	10
Plastics processing	6
All other	7
	100

(G25)

Consumer Product Information:

Category	No. of products containing dichloromethane	$\frac{\text{No. of dichloromethane products in category}}{\text{Total no. of products in category}}$ x 10
Cleaning agents and compounds	3	0.17%
Paints, varnishes, shellac, rust preventatives, etc.	41	0.37%
Household aerosols	1,298	34.55%
Solvent-based cleaning and sanitizing agents	8	3.67%
Caustics, lyes and drain cleaners	2	0.87%
Adhesives and adhesive products, including glue	4	0.75%
Paint and varnish removers	2	18.18%

The 1,358 products surveyed contained an average of 30.0% dichloromethane.

(G27)

1.6 Exposure Estimates

1.6.1 Release Rate: 367.0 million lb (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 57

Estimated no. of persons exposed: 2,499,000

(G29)

1.7 Manufacturers

Allied Chemical Corp.
Diamond Shamrock Corp.
Dow Chemical Corp.
Stauffer Chemical Co.
Vulcan Materials Co.

(G24)

DICHLOROMETHANE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Dichloromethane's high vapor pressure (440 mm at 25°C (G38)) facilitates its excretion unchanged via the lungs. In addition, its stability and water solubility (13 g/liter (G14)) promote excretion in the urine. Experiments verify that the compound is largely excreted unchanged by the lungs (G38), especially when subjects are exposed under occupational conditions (to dichloromethane at about 200 ppm).

DiVincenzo and Hamilton (38) reported no accumulation of radioactivity in rats administered labeled dichloromethane intraperitoneally.

Only minor portions of an intraperitoneal dose are metabolized to carbon dioxide, carbon monoxide, and an unidentified urinary metabolite (38). Pearson and McConnell (14) found no evidence for the bioaccumulation of C_1/C_2 chlorinated hydrocarbons in food chains in a marine environment.

2.2 Impurities and Environmental Degradation or Conversion Products

Impurities found in commercial dichloromethane include chloroform (up to 2,500 ppm), methyl chloride, cyclohexane, water (up to 200 ppm), acid (HCl, up to 5 ppm), and trans-dichloroethene (G14,G17). A sample of dichloromethane used in a Russian cellulose acetate factory was stated to contain 0.25%

methyl chloride, 0.25% chloroform, and 1% ethanol (3, as reported in 15). The commercial chemical often contains a small amount (0.0001%) of an additive such as phenol, hydroquinone, p-cresol, resorcinol, thymol, and 1-naphthol, or small quantities of amines to stabilize it during contact with air and moisture (G17).

Methylene chloride is stated to be one of the most stable of the chloroparaffins (G17). It is only slightly reactive toward the hydroxyl radical (half-life about 1 year) and much less so toward the peroxy radical and ozone; it is also highly resistant to hydrolysis (half-life about 700 years) (G14). Spence et al. (24) reported that the photo-oxidation of the compound in the troposphere probably proceeds with a half-life of several months. They irradiated 20 ppm dichloromethane at 1 atmosphere pressure and obtained carbon dioxide and carbon monoxide as the major carbon-containing products. They also observed hydrochloric acid and a small amount of phosgene. In similar experiments, Pearson and McConnell (14) obtained the same products, with the exception of phosgene. They estimated the tropospheric half-life of dichloromethane, based on outdoor exposure in quartz flasks, to be 33 weeks.

No information on biodegradation was found (G14).

2.3 Acute Toxicity

The acute toxicity of dichloromethane, as reported in the NIOSH Registry of Toxic Effects of Chemical Substances (G16), is given in Table IV-1.

TABLE IV-1

Acute Toxicity of Dichloromethane

Parameter	Dosage	Species	Route
TCLo	500 ppm/8 hr	Human	Inhalation
LD50	2,136 mg/kg	Rat	Oral
"	1,500 mg/kg	Mouse	Intraperitoneal
"	6,460 mg/kg	"	Subcutaneous
"	3,000 mg/kg	Dog	Oral
"	950 mg/kg	"	Intraperitoneal
"	2,700 mg/kg	"	Subcutaneous
"	200 mg/kg	"	Intravenous
"	1,900 mg/kg	Rabbit	Oral
"	2,700 mg/kg	"	Subcutaneous
LCLo	5,000 ppm/2 hr	Guinea Pig	Inhalation

Svirbely et al. (13, as cited in 15) determined the LC50 in mice for a 7-hour inhalation exposure to be 16,188 ppm.

Gradiski et al. (25) found an LD50 of 1,900 mg/kg in female mice treated intraperitoneally.

Kimura et al. (26) reported oral LD50's of <1.00 ml/kg in newborn rats and 1.8, 1.6, and 2.3 ml/kg in 14-day-old, young adult, and older rats, respectively.

Aviado and Smith (32) reported that guinea pigs exposed to this chemical for 6 hours had mortality rates of 15% at 8,700 ppm, 40% at 11,100 ppm, and 100% at 16,000 ppm. Increased levels of triglycerides and carboxyhemoglobin were also observed.

Aviado (27) classified dichloromethane as a highly toxic, low pressure propellant. Its inhalation at concentrations of 0.5-5% by monkeys and dogs and at 1-10% by rats and mice was reported to cause major adverse effects on the lungs and heart, including cardiac arrhythmia and tachycardia.

In humans, accidental ingestion of dichloromethane preparations, such as paint remover, has reportedly caused unconsciousness, acidosis, and hemoglobinuria (28). Stewart and coworkers reported finding elevated carboxyhemoglobin levels in human subjects exposed by inhalation for 2 hours to dichloromethane at 500-1,000 ppm (29,30) and in humans exposed to paint removers containing dichloromethane (31). Humans exposed to dichloromethane at 1,000 ppm for 2 hours showed carboxyhemoglobin saturation levels in excess of those permitted from occupational exposure to carbon monoxide (30).

Other experiments have demonstrated that exposure at 25,000 ppm for 2 hours was not lethal (G4). Exposure at 7,200 ppm caused paresthesia of the extremities in 8 minutes and increased pulse rate, congestion in the head, a sensation of heat, and mild eye irritations. Exposure at 2,300 ppm for 1 hour caused nausea after 30 minutes.

2.4 Other Toxic Effects

Dichloromethane was described as an irritant and weak narcotic (G3). When used as an anesthetic in humans, it caused stertorous breathing, cyanosis, dilated pupils, and a rapid weak pulse. Hyperbilirubinemia and reduced albumin-globulin ratio after mild occupational poisoning with dichloromethane have been reported (G10). Rats, rabbits, and dogs, but not guinea pigs tolerated exposure by inhalation at 5,000 ppm (17 mg/liter), 7 hours/day, 5 days a week, for 6 months (G3).

Reported toxic effects of repeated exposure to mammals included liver damage in mice, dogs, monkeys, and rats; reduced growth rates in monkeys and rats; brain damage in mice; liver enzyme alterations in rats; and death in mice and dogs (G14,G15).

Weinstein et al. (17) observed that continuous inhalation of dichloromethane at 5,000 ppm by female mice induced polyribosomal dissociation and swelling of hepatocyte rough endoplasmic reticulum, which showed partial reversal after 2 days. Other findings were transient fatty changes (increase in triglycerides) and partial inhibition of leucine incorporation in liver protein.

Aviado and Smith (32) reported that exposure to dichloromethane as an aerosol propellant did not alter respiratory minute volume in monkeys but affected pulmonary resistance and compliance.

Balmer et al. (33) detected increased triglyceride levels in guinea pigs exposed at 552-679 ppm for 5 days. Guinea pigs exposed once at 11,100 ppm were said to have congestion and hemorrhage in the lungs and centrilobular patchy fat vacuolation. Five days of exposure at 552-679 ppm induced fatty changes in the liver and some pneumonitis. Not all the guinea pigs were affected. Ballantyne et al. (34) reported transient effects such as inflammation of the conjunctiva and eyelids and increased corneal thickness and intraocular tension in rabbits exposed to dichloromethane as a liquid or vapor.

Johnson (35) detected 100% increases in glutathione levels in female rats given 11.8 millimoles/kg of dichloromethane orally and killed 2 hours later.

Gamberale et al. (36) investigated the effect of dichloromethane on reaction time, short-term memory, and numerical ability in 14 healthy men exposed at 870-3,470 mg/m^3. Irregularity of response was evident in subject reaction time only at the highest concentration. Other toxicity data are summarized in Tables IV-2 and IV-3, which were adapted from the NIOSH criteria document (15).

The ACGIH Threshold Limit Value (TLV) for dichloromethane is 200 ppm (G11).

2.5 Carcinogenicity

It has been reported that no tumors developed in dogs, rabbits, guinea pigs, and rats exposed by inhalation for up to 6 months at 5,000 ppm (17 mg/liter) for 7 hours/day, 5 days a week, and at 10,000 ppm (34 mg/liter) for 4 hours/day, 5 days a week (G18).

2.6 Mutagenicity

No information on mutagenicity was found in the sources searched.

TABLE IV-2

EFFECTS OF ACUTE INHALATION EXPOSURE TO DICHLOROMETHANE

Animal	Concentration (ppm)	Duration	Effects	Reference Cited
Human	317 and 751	4 hr	Depressed critical flicker frequency (CFF), auditory vigilance performance	8
"	317, 470, and 751	3-5 hr	Decreased performance of CFF, auditory vigilance, psychomotor tasks	9
"	Unknown	4 hr	Oppressive odor, eye irritation, excessive fatigue, weakness, sleepiness, lightheadedness, chilly sensations, nausea, shortness of breath, substernal pain, weakness, dry rales in chest, pulmonary edema	11
Mouse	14,500	2 hr	Death	12
"	10,000	2 hr	Narcosis	12
"	5,000	7 days	Initial increase in physical activity followed by decrease in food and water intake, lethargy, increased liver-to-body weight ratio and liver fat, mild fatty infiltrations, hydropic degeneration of centrilobular cells	17
"	100	Up to 10 wk continuous	Elevated liver fat, decreased hepatocyte glycogen, centrilobular fatty infiltration	18

TABLE IV-2 (continued)

EFFECTS OF ACUTE INHALATION EXPOSURE TO DICHLOROMETHANE

Animal	Concentration (ppm)	Duration	Effects	Reference Cited
Mouse	25	14 wk continuous	Increased activity	16
Rat	25,000 to 28,000	1.5 hr	Cessation of electrical activity after 1.5 hr	22
"	16,000-18,000	6 hr	Initial excitement followed by deep narcosis, decreased EMG tonus, decreased EEG activity, breathing difficulties, tremor, cessation of electrical activity after 6 hr	22
"	5,000 to 9,000	8 hr	Long sleeping phase lacking desynchronization phases	22
"	3,000, 1,000, and 500	24 hr	Suppressed REM sleep, increased time between two REM periods, linear relation between dose and response	8
"	2,800	14 hr	Decreased proportion of REM sleep to total sleep	22
"	100 or 1,000	3 hr	Increased blood CO	23
Dog	40,000	-	Loss of pupillary and corneal reflexes after 10-20 min, complete muscular relaxation after 16 min, death from progressive heart failure due to cardiac injury in 3 of 5 dogs	21

TABLE VI-2 (continued)

EFFECTS OF ACUTE INHALATION EXPOSURE TO DICHLOROMETHANE

Animal	Concentration (ppm)	Duration	Effects	Reference Cited
Dog	15,000 and 20,000	-	Loss of pupillary and corneal reflexes after 10-20 min, complete muscular relaxation after 25-35 min, reduction in blood pressure and rapid narcosis at 20,000 ppm	21
"	6,000	6 hr	Light narcosis in 2 hr	12
"	4,000	"	Light narcosis after 2.5 hr	12
Mouse, rat, monkey, dog	5,000	14 wk continuous	High mortality, pneumonia, fatty liver, icterus, splenic atrophy, edema of meninges, renal tubule vascular changes	20
"	1,000	"	Increased hematocrit, Hgb, RBC, bilirubin, weight loss; mild centrilobular fat	20
"	100	2-8 wk continuous	Altered cytochromes P-450, P-420, and b5; fatty infiltration of the liver; nonspecific tubular degenerative and regenerative changes: elevated COHb	19
"	25	"	No overt toxicity, nonspecific tubular degenerative and regenerative changes	19

TABLE IV-2 (continued)

EFFECTS OF ACUTE INHALATION EXPOSURE TO DICHLOROMETHANE

Animal	Concentration (ppm)	Duration	Effects	Reference Cited
Rabbit	6,000	6 hr	Light narcosis in 45 min	12
"	4,000	"	Light narcosis after 6 hr	12
Guinea pig	6,000	"	Light narcosis in 2.5 hr	12
Cat	6,000	"	Light narcosis in 45 min	12

Adapted from NIOSH Criteria for a Recommended Standard--Occupational Exposure to Methylene Chloride (15)

TABLE IV-3

EFFECTS OF REPEATED INHALATION OF DICHLOROMETHANE

Animal	Concentration (ppm)	Duration	Observations	Reference Cited
Human	50-500	7.5 hr/day 5 days/wk	Increased affinity of Hgb for oxygen in proportion to exposure concentration	1
"	100 and 500	"	Slightly increased blood lactic acid from exercise at 500 ppm,	1
Human (1 subject)	Unknown	13 yr intermittent	Irregular, severe leg and arm pains, hot flashes, vertigo , stupor, poor night vision, anorexia, precordial pain, rapid pulse, shortness of breath, fatigue, attacks of rapid heartbeat	2
Human (1 worker)	Unknown	20 yr intermittent	Drowsy, pains in head, tingling in hands and feet	2
Human (33 workers)	28-4,896	Average of 2 yr exposure	Headache, fatigue, irritation of upper respiratory tract, conjunctiva, neurasthenic disorders, mild acute poisoning in 3 with unconsciousness in 1, sweet taste, heart palpitations	3

TABLE IV-3 (continued)

EFFECTS OF REPEATED INHALATION OF DICHLOROMETHANE

Animal	Concentration (ppm)	Duration	Observations	Reference Cited
Human (1 worker)	660-3,600	Several hr/day for 5 yr	After 3 yr, burning pain around heart, restlessness, feeling of pressure, palpitations, forgetfulness, insomnia, and feeling of drunkenness; after 5 yr auditory and visual hallucinations, slight erythema of hands and underarms, encephalosis diagnosed	4
Human (4 workers)	159-219 (average 183)	8 hr/day, 6 days/wk for several yr	Increased alveolar CO at end of workday	5
Rat	5,000	30 min/day on 5 alternate days	Decreased running activity	6
Dog, rabbit, guinea pig, rat	5,000	7 hr/day 5 days/wk up to 6 mo	No effect	7
Dog, monkey, rabbit, guinea pig, rat	10,000	4 hr/day 5 days/wk for 8 wk	Incoordination, conjunctival irritation, shallow respiration, pulmonary congestion, edema with focal extravasation of blood, some fatty degeneration	7

Adapted from NIOSH Criteria for a Recommended Standard --Occupational Exposure to Methylene Chloride (15)

2.7 Teratogenicity

Schwetz et al. (37) reported finding no fetal toxicity or teratogenicity when pregnant rats and mice were exposed to dichloromethane at 2,450 ppm for 7 hours/day during gestation. However, they did find an increased incidence of extra or split sternebrae in offspring from mice and rats exposed at 1,250 ppm.

2.8 Metabolic Information

DiVincenzo and Hamilton (38) studied the metabolic fate of dichloromethane. In 24 hours, about 91% of ^{14}C-dichloromethane administered to rats intraperitoneally at 412-930 mg/kg was eliminated in the breath unchanged, 2% as carbon monoxide, 3% as carbon dioxide, and 1.5% as unidentified metabolite. Urine contained 1% and the carcass 2% of the radioactivity. The highest tissue activity was found in liver, kidney, and adrenals. Formaldehyde levels were increased in serum but decreased in tissue, and there was no evidence that dichloromethane was metabolized to formaldehyde. The authors suggested that formation of carbon monoxide might occur by enzymatic action of the microsomal heme-oxygenase system.

Kassebart and Angerer (49, as reported in 15) have proposed a mechanism for the metabolism of dichloromethane. They suggested that the parent compound might be converted into formaldehyde by hydrolytic dehydrochlorination. The formaldehyde would be oxidized to formic acid, which would be oxidized to carbon dioxide and water and dehydrated to carbon monoxide and water.

Carlson and Hultengren (39) investigated the relationship between methylene chloride exposure and the concentration of carboxyhemoglobin and carbon monoxide in the blood. Rats were exposed to ^{14}C-dichloromethane at 1,935 mg/m^3 in inspiratory air. The results showed that the level of carboxyhemoglobin was increased due to carbon monoxide derived from methylene chloride. The highest concentrations of dichloromethane or its metabolites per gram of tissue were detected in the white adipose tissue. The concentration in adipose tissue declined by 90% in 2 hours, whereas in the liver and brain, the levels dropped by 25% and 75%, respectively, during the same time.

In preliminary in vitro and in vivo metabolism studies, Hogan et al. (40) also have reported microsomal conversion of dichloromethane to carbon monoxide.

Recently Rodkey and Collison (41) reported biological oxidation of ^{14}C-dichloromethane to carbon monoxide and carbon dioxide in the rat. The authors suggested that this halogenated hydrocarbon acted as a direct substrate and was metabolized to carbon monoxide. Settle (42) had suggested earlier that increased carboxyhemoglobin levels seen in vivo are due to a change in carbon monoxide affinity rather than dichloromethane metabolism.

Ratney et al. (43) reported that dichloromethane was converted to carbon monoxide and blood carboxyhemoglobin levels were elevated in humans exposed to about 280 ppm for 8 hours. Stewart et al. (29) reported the same findings in studies with humans exposed to 500-1,000 ppm for 1-2 hours.

Stewart and Dodd (44) reported that immersion of a human thumb in dichloromethane resulted in a mean peak breath concentration of 3.1 ppm in 30 minutes and mean breath concentration of 0.69 ppm after 2 hours.

2.9 Environmental Release and Ecological Effects

An extroardinarily large volume of dichloromethane enters the environment on a regular basis. Indeed, the Stanford Research Institute estimated that in 1972 95% of its uses were dispersive. Because of the pattern of its uses (paint remover, aerosol spray, etc.), much of the chemical is released into the home and the factory (G14). It is also reported to be used as a food additive (G4).

The compound has been detected at 8 ppb in water by gas chromotography/mass spectrometry (G14). EPA has reported dichloromethane concentrations in waste water effluents in the 100 ppm range. In a survey of municipal water in sites in EPA Region V (upper Midwest), 7 of 83 sites tested contained dichloromethane at levels as high as 7 ppb (45).

The compound is reported to be nontoxic to sewage infusoria and flagellates at concentrations up to 2,000 mg/liter and to sewage nitrifiers at concentrations up to 2,500 mg/liter (G14). On the other hand, studies have been cited (45) in which the interaction of chloromethanes (including dichloromethane) with anaerobic organisms has resulted in inhibition in various digestive systems, e.g., sewage, sludge, and rumen of cow.

The Aquatic Toxicity Rating (96-hr TLm, species unspecified) is 1,000-100 ppm, which indicates that it is ranked as practically nontoxic (G16).

No reports of ecological incidents involving dichloromethane were found in the sources searched, although some concern has been expressed about possible inhibition of natural fermentation processes (45).

Between December 1974 and February 1975, <5 ppt of the compound were found in the air of a rural area near Pullman, Washington (46). Analyses of the atmosphere, fresh water, sea water, marine sediments, algae, invertebrates, fish, and other aquatic life in the Liverpool Bay area of England were negative for dichloromethane (14). A 1978 document on halomethanes states that atmospheric concentrations of methylene chloride are abo 35 ppt above marine and land areas except urban areas, where concentrations range from less than 20 to 144 ppt (45).

There are descriptions of the effects that the chemical has had on the health of workers who were exposed at various concentrations (15). In one workplace, air samples taken over a 2-day period averaged 391 ppm of dichloromethane (43, as reported in 15). In a Russian factory, levels over a 3-year period were reported to range from 30 to 5,000 ppm with an average of 627 ppm (50, as reported in 15). A survey (45) revealed concentrations of the chemical in the 4-20 ppb range associated with the indoor atmosphere of certain business establishments open to the public.

2.10 Current Testing

Dow Chemical Company is currently testing dichloromethane for carcinogenicity in a 2-year inhalation study at the Toxicology Research Laboratory at Midland, Michigan. Rats and hamsters are being exposed at 500, 1,500, and 3,500 ppm for 6 hours/day, 5 days/week. Results are expected in mid-1978 (47,48).

The National Cancer Institute is sponsoring a 2-year study with mice and rats (administration by gavage), which began in June 1976 with prechronic-testing. In addition, NCI has selected dichloromethane for a 2-year inhalation study with rats and mice. In both of these studies, all animals will be killed and their tissues examined histopathologically, but no clinical chemistry, mutagenic, or teratogenic evaluations will be performed (G12,47).

The University of Arizona is planning to study the bioactivation of some halogenated alkanes and alkenes, including dichloromethane, and their covalent binding to tissue macromolecules. Tests will be performed in various strains of mice, rats, and hamsters (10).

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HALOGENATED ALKYL EPOXIDES

AN OVERVIEW

The seven epoxides included in this dossier are halogenated noncyclic aliphatic hydrocarbons with one or more epoxy functional groups. The specific substances are 1-chloro-2,3-epoxypropane (epichlorohydrin), 1,1,1-trichloro-2,3-epoxypropane (TCPO), 1-bromo-2,3-epoxypropane (epibromohydrin), 1,4-dichloro-2,3-epoxybutane, 1,1,1-trichloro-3,4-epoxybutane (TCBO), tetrafluoroethylene epoxide (TFEO), and hexafluoropropylene epoxide (HFPO). Several of these compounds are liquids that are generally more soluble in organic solvents than in water.

Over 500 million pounds of epichlorohydrin were produced in the United States in 1975. No accurate production figures for epibromohydrin were found, but its estimated annual production is between 1 thousand and 1 million pounds. Apparently, only limited amounts of the other halogenated epoxides are produced.

Epichlorohydrin is used extensively as an intermediate and solvent in the manufacture of various products, including glycerine, epoxy resins, paints, varnishes, shellacs, flame-retardant chemicals, and household aerosols. TCPO is used in research laboratories as an inhibitor of the enzyme epoxide hydrase. TCBO has potential uses as an intermediate in the preparation of urethane, epoxy resins, phenolic resins, and many other chemicals. No information on the uses of epibromohydrin and 1,4-dichloro-2,3-epoxybutane was found. TFEO and HFPO are monomers used in the production of specific polymers.

NIOSH estimates that between 50,000 and 140,000 workers in the United States are occupationally exposed to epichlorohydrin. No exposure estimates on the other epoxides were found.

No reports on the bioaccumulation and ecological effects of these epoxides were found in the sources searched.

Severe necrotic lesions have occurred in humans after skin contact with epichlorohydrin, and humans exposed to the chemical at a high atmospheric concentration have experienced eye and throat irritation, nausea, dyspnea, bronchitis with bronchiolar constrictions, and enlarged livers. TCBO causes skin and eye irritation in rabbits. Results of carcinogenicity studies on epichlorohydrin are equivocal. No lesions were observed in animals exposed by skin application, but subcutaneous injections induced sarcoma and adenosarcoma. TCPO inhibits detoxifying enzymes in mammals and potentiates the effect of carcinogens. Negative results for carcinogenicity were reported for epibromohydrin and TCPO when applied dermally.

Epichlorohydrin has been shown to be mutagenic in mice and bacteria; positive results were also reported for epibromohydrin and TCBO. Increased embryolethality in animals exposed to TCPO and antifertility effects in animals exposed to epichlorohydrin have been reported. No reports of teratogenic effects from these epoxides were found in the sources searched.

HALOGENATED ALKYL EPOXIDES

PART I

GENERAL INFORMATION

1-CHLORO-2,3-EPOXYPROPANE (EPICHLOROHYDRIN)

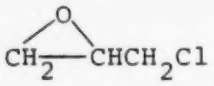
1.1 Identification
CAS No.: 000106898
NIOSH No.: TX49000

1.2 Synonyms and Trade Names

3-Chloro-1,2-epoxypropane; (chloromethyl)ethylene oxide; chloromethyloxirane; chloropropylene oxide; gamma-chloropropylene oxide; 3-chloro-1,2-propylene oxide; alpha-epichlorohydrin; epichlorohydrin; glycerol epichlorohydrin; oxirane,(chloromethyl)-; oxirane, 2-(chloromethyl)-

(G16)

1.3 Chemical Formula and Molecular Weight



$CH_2\overset{O}{-}CHCH_2Cl$

C_3H_5OCl Mol. wt. 92.53

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Highly volatile, unstable liquid; chloroform-like odor
(G23)

1.4.2 Boiling Point: 116.5°C (G22)

1.4.3 Melting Point: -48°C (G22)

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure: 12.5 mm at 20°C (G22)

1.4.6 Solubility: Slightly soluble in water; soluble in benzene; soluble in all proportions in alcohol and ether

(G22)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production:		
	340 million lb (1973)	(G41)
	495 million lb (1974)	(G15)
	550 million lb (1975)	(G19)

1.5.2 Use: Major raw material for epoxy and phenoxy resins; in the manufacture of glycerol; for curing propylene-based rubbers; solvent for cellulose esters and ethers; in high wet-strength resins for paper industry

(G21)

Consumer Product Information:

Category	No. of products containing 1-chloro-2,3-epoxy propane	$\frac{\text{No. of products containing 1-chloro-2,3-epoxy propane}}{\text{Total no. of products in category}} \times 100$
Paints, varnishes, shellac, rust preventatives, etc.	4	0.04%
Flame-retardant chemicals	1	0.17%
Household aerosols	5	0.13%

The 10 products surveyed contained an average of 6.7% 1-chloro-2,3-epoxy propane.

(G27)

Quantitative Distribution (1970):

Glycerin manufacture	55%
Epoxy resins	40
Miscellaneous	5
	100%

(G25)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information was found in the sources searched.

1.6.2 NIOSH Estimates of Occupational Exposure:

NOHS Rank: 882

Estimated no. of persons exposed: 140,000*

*rough estimate

(G29)

In its criteria document, NIOSH estimated that 50,000 workers are occupationally exposed to epichlorohydrin in the United States (1).

1.7 Manufacturers

Dow Chemical USA
Shell Chemical Co. (G25)

1,1,1-TRICHLORO-2,3-EPOXYPROPANE (TCPO)

1.1 Identification

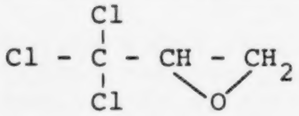
CAS No.: 003083236
NIOSH No.:

1.2 Synonyms and Trade Names

1,2 epoxy-3,3,3 trichloropropane;
3,3,3-trichloropropylene oxide; TCPO

(G22,G30)

1.3 Chemical Formula and Molecular Weight



$C_3H_3Cl_3O$ Mol. wt. 161.42

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: No information was found in the sources searched.

1.4.2 Boiling Point: 149°C at 764 mm

(G22)

1.4.3 Melting Point: No information was found in the sources searched.

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure:

No information was found in the sources searched.

1.4.6 Solubility: Very soluble in ether

(G22)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production: Only known production is as a laboratory chemical.

1.5.2 Use: Research chemical--an inhibitor of the enzyme epoxide hydrase

(G30)

1.6 Exposure Estimates

No information was found in the sources searched.

1.7 Manfacturers

Aldrich Chemical Co., Inc.	(G30)

1-BROMO-2,3-EPOXYPROPANE (EPIBROMOHYDRIN)

1.1 Identification

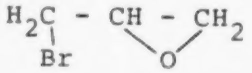
CAS No.: 003132647
NIOSH No.:

1.2 Synonyms and Trade Names

Epibromohydrin

(G22)

1.3 Chemical Formula and Molecular Weight



C_3H_5BrO Mol. wt. 136.98

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description:

No information was found in the sources searched.

1.4.2 Boiling Point: 138-140°C

(G22)

1.4.3 Melting Point: -40°C

(G30)

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure:

No information was found in the sources searched.

1.4.6 Solubility:

Insoluble in water; soluble in hot alcohol, ether, benzene, and chloroform

(G22)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production:

Estimated production is between 1,000 and 1,000,000 lb (1976).

(G41)

1.5.2 Use:

No information was found in the sources searched.

1.6 Exposure Estimates

No information was found in the sources searched.

1.7 Manufacturers and Suppliers

Aldrich Chemical Co., Inc.
Freeman Industries, Inc.
Great Lakes Chemical Corp.

(G30, G37)

1,4-DICHLORO-2,3-EPOXYBUTANE

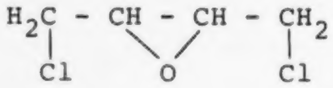
1.1 Identification

CAS No.: 003583479
NIOSH No.: EJ80500

1.2 Synonyms and Trade Names

No information was found in the sources searched.

1.3 Chemical Formula and Molecular Weight



$C_4H_6Cl_2O$ Mol. wt. 141.00

(G16)

1.4 Chemical and Physical Properties

No information was found in the sources searched.

1.5 Production and Use

No information was found in the sources searched.

1.6 Exposure Estimates

No information was found in the sources searched.

1.7 Manufacturers

No information was found in the sources searched.

1,1,1-TRICHLORO-3,4-EPOXYBUTANE (TCBO)

1.1 Identification

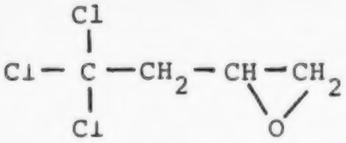
CAS No.: 003088258

NIOSH No.:

1.2 Synonyms and Trade Names

Trichlorobutylene oxide; butane, 1,1,1-trichloro-3,4-epoxy-; oxirane, (2,2,2-trichloroethyl)-; 4,4,4-trichloro-1,2-epoxybutane; 4,4,4-trichloro-1,2-butylene oxide; TCBO (2)

1.3 Chemical Formula and Molecular Weight



$C_4H_5Cl_3O$ Mol. wt. 175.4 (2,3,4)

1.4 Chemical and Physical Properties

1.4.1 Description: Dark amber liquid (2,3)

1.4.2 Boiling Point: 174°C (3)

1.4.3 Melting Point: No information was found in the sources searched.

1.4.4 Absorption Spectrometry: No information was found in the sources searched.

1.4.5 Vapor Pressure: No information was found in the sources-searched.

1.4.6 Solubility: Insoluble in water; miscible with common organic solvents such as carbon tetrachloride, chloroform, and benzene (2,3)

1.4.7 Octanol/Water Partition Coefficient:

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production: No information was found in the sources searched.

1.5.2 Use: Not known if TCBO is used commercially at this time, but has potential uses as an intermediate in the preparation of urethanes, epoxy resins, and esters; in fire-retarding phenolic resins; as a neutralizing agent; in insecticides, fungicides, nematocides; as an olefinic polymerization activator; in glycols, plasticizers, and modifiers; in textiles; in the vulcanization of graft polymer rubbers

(2,4)

1.6 Exposure Estimates

No information was found in the sources searched.

1.7 Manufacturers and Suppliers

Olin Chemicals	(2,3,4)

TETRAFLUOROETHYLENE EPOXIDE (TFEO)

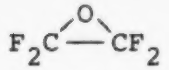
1.1 Identification

CAS No.:
NIOSH No.:

1.2 Synonyms and Trade Names

TFEO (G21)

1.3 Chemical Formula and Molecular Weight



C_2F_4O Mol. wt. 116.01 (G21)

1.4 Chemical and Physical Properties

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production:

No information was found in the sources searched.

1.5.2 Use:

In the synthesis of TFEO dimers and polymers (e.g., Freon E, the trademark for a series of TFEO polymers used as coolants in electronic devices) (G21)

1.6 Exposure Estimates

No information was found in the sources searched.

1.7 Manufacturers

No information was found in the sources searched.

HEXAFLUOROPROPYLENE EPOXIDE (HFPO)

1.1 Identification

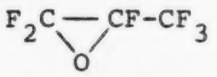
CAS No.: 000428591
NIOSH No.:

1.2 Synonyms and Trade Names

HFPO; propane, 1,2-epoxy-1,1,2,3,3,3-hexafluoro-; oxirane, trifluoro(trifluoromethyl)-; hexafluoropropylene oxide; hexafluoropropene oxide; perfluoropropylene oxide; propylene oxide hexafluoride

(G21,48)

1.3 Chemical Formula and Molecular Weight



C_3F_6O Mol. wt. 166.02

1.4 Chemical and Physical Properties

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production:

No information was found in the sources searched.

1.5.2 Use:

In the synthesis of HFPO polymers (e.g., Krytox, the trademark for a series of HFPO polymers used as lubricating oils and greases) (G21)

1.6 Exposure Estimates

No information was found in the sources searched.

1.7 Manufacturers

No information was found in the sources searched.

TABLE V-1

CHARACTERISTICS OF HALOGENATED ALKYL EPOXIDES

Name	Solubility	Log P_{oct}	Estimated Environmental Release (million lb)	Estimated No. of Persons Exposed (Occupational)	Use
1-Chloro-2,3-epoxypropane (Epichlorohydrin)	ss in H_2O; s in bz; ∞ in alc and eth	*	*	~140,000	In manufacture of glycerol and epoxy resins, in paints and household aerosols and as flame retardant
1,1,1-Trichloro-2,3-epoxypropane (TCPO)	vs in eth	*	*	*	Research chemical--an inhibitor of the enzyme epoxide hydrase
1-Bromo-2,3-epoxypropane (Epibromohydrin)	i in H_2O; s in hot alc, eth, bz, and chl	*	*	*	*
1,4-Dichloro-2,3-epoxybutane	*	*	*	*	*

TABLE V-1 (continued)

Name	Solubility	Log P_{oct}	Estimated Environmental Release (million lb)	Estimated No. of Persons Exposed (Occupational)	Use
1,1,1-Trichloro-3,4-epoxybutane (TCBO)	i in H_2O; ∞ in CCl_4, chl, and bz	*	*	*	Potential uses in resins, pesticides; as a neutralizing agent; in olefinic polymerization; in glycols, plasticizers, textiles; in vulcanization of graft polymer resins
Tetrafluoroethylene epoxide (TFEO)	*	*	*	*	In synthesis of TFEO dimers and polymers (e.g. Freon E, the trademark for a series of TFEO polymers used as coolants in electrical devices)
Hexafluoropropylene epoxide (HFPO)	*	*	*	*	In the synthesis of HFPO polymers (e.g. Krytox, the trademark for a series of HFPO polymers used as lubricating oils and greases)

*No information was found in the sources searched.

Key to Abbreviations:
i -- insoluble
s -- soluble
ss -- slightly soluble
vs -- very soluble
∞ -- soluble in all proportions
alc -- alcohol
bz -- benzene
chl -- chloroform
eth -- ether

HALOGENATED ALKYL EPOXIDES

PART II

BIOLOGICAL PROPERTIES

1-CHLORO-2,3-EPOXYPROPANE (EPICHLOROHYDRIN)

2.1 Bioaccumulation

No data on the bioaccumulation of epichlorohydrin were found in the sources searched. Theoretically, the high chemical reactivity of the halo substituent and of the epoxy group lessens the possibility of bioaccumulation.

2.2 Impurities and Environmental Degradation or Conversion Products

The impurities in 1-chloro-2,3-epoxypropane (epichlorohydrin) depend on the method of manufacture. In the most common method, allyl chloride from high-temperature chlorination of propylene is chlorohydrogenated with chlorine water to give glycerol chlorohydrin isomers. This mixture is dehydrochlorinated with alkali, and epichlorohydrin is recovered by steam distillation. In this process, allyl alcohol, 3-chloro-1,2-propylene glycol, and water are potential impurities. About 47% of the epichlorohydrin produced is immediately used in crude form to make synthetic glycerine. The remainder is refined and used as a chemical intermediate, mostly for polymer production (G41).

The ring of the reactive epoxide group opens when epichlorohydrin reacts with acid (G17). Epichlorohydrin also reacts with compounds having active hydrogens, e.g., alcohols, water, organic acids, phenols, thiols, and amines. The chloro group, being allylic to the epoxide or a hetero group (after ring opening), will also be reactive.

2.3 Acute Toxicity

The acute toxicity of epichlorohydrin, as reported in the NIOSH Registry of Toxic Effects of Chemical Substances (G16), is given in Table V-2.

TABLE V-2

ACUTE TOXICITY OF EPICHLOROHYDRIN

Parameter	Dosage	Animal	Route
TCLo (eye effects)	20 ppm	Human	Inhalation
LCLo	250 ppm/4 hr	Rat	"
"	7,400 ppm/30 min	Mouse	"
LD50	90 mg/kg	Rat	Oral
"	238 mg/kg	Mouse	"
"	155 mg/kg	"	Intra-peritoneal
"	1,300 mg/kg	Rabbit	Skin

Epichlorohydrin has been described as irritating, especially to the eyes, and moderately systemically toxic by the inhalation, oral, percutaneous, and subcutaneous routes (G38).

Humans exposed to epichlorohydrin at an unspecified high atmospheric concentration were reported to have had irritation of the eyes and throat, nausea, dyspnea, bronchitis with bronchiolar constrictions, and enlarged livers (G38).

A summary of acute toxicity data from the NIOSH criteria document on epichlorohydrin appears in Table V-3 (1).

2.4 Other Toxic Effects

Secondary sources reported that death in animals exposed to epichlorohydrin (details unspecified) is generally due to depression of the central nervous system, particularly the respiratory center, and irritation of the respiratory tract (G38).

Impairment of kidney function in animals has been attributed to epichlorohydrin exposure, and the cumulative effects of repeated exposure are considered to be caused by nephrotoxic actions (G38,G9).

Epichlorohydrin has been reported to penetrate human skin and induce systemic effects. Severe necrotic lesions were observed after a latency period of several minutes to several hours (13, as reported in 1).

Hahn (14)reported that oral administration of epichlorohydrin at 15 mg/kg to male rats for 12 days produced reversible infertility as determined by the decreased number of uterine implants in females after mating.

Cooper et al. (15, as reported in 1) reported permanent infertility in male rats fed epichlorohydrin. Five rats fed 100 mg/kg over 5 consecutive days (20 mg/kg/day) were infertile for the next 2 weeks, but regained their fertility in the 3rd week. Five rats fed a single dose each of epichlorohydrin at 100 mg/kg developed similar temporary infertility. During

TABLE V-3

EFFECTS OF ACUTE EXPOSURE TO EPICHLOROHYDRIN IN ANIMALS

Route	Animal	No.	Exposure	Observations	References Cited
Inhalation	Mouse	30	16,600 ppm 30 min	Nose and eye irritation; 100% mortality	5
"	"	20	8,300 ppm 30 min	100% mortality	5
"	"	30	2,370 ppm 1 hr	No deaths	5
"	Rat	6	250 ppm 4 hr	Death of 2-4 rats	6
"	"	60	91.0 ppm 4 hr	Kidney damage, liver function disrupted	7
"	"	60	5.2 ppm 4 hr	"	7
"	"	60	1.8 ppm 4 hr	Kidney damage and disrupted liver function less severe than at 91.0 and 5.2 ppm	7
Subcutaneous	"	120	500 mg/kg 250 mg/kg 125 mg/kg	Reduced blood histamine activity	7
"	"	14	180 mg/kg	Necrotic lesions in nephrons; non-specific lung, brain, and adrenal gland damage	9
"	"	23	150 mg/kg	"	9

TABLE V-3 (continued)

Route	Animal	No.	Exposure	Observations	References Cited
Subcutaneous	Rat	-	150 mg/kg	LD50	10
"	"	67	125 mg/kg	Oliguria, anuria, polyuria, kidney damage	11
"	Mouse	10	0.23 ml/kg/day 4 days	100% mortality	5
"	"	10	0.08 ml/kg/day 21 days	"	5
Oral	"	15	0.5 ml/kg	"	5
"	"	15	0.23 ml/kg/day 4 days	"	5
"	"	15	0.08 ml/kg/day 21 days	"	5
"	"	15	0.23 ml/kg	No deaths	5
"	"	-	0.20 ml/kg	LD50	12
"	Rat	-	0.22 ml/kg	"	12
Dermal	Rabbit	-	0.64 ml/kg	"	12
"	Rat	20	2 ml/kg 1 hr	Local irritation, 90% mortality	5
"	"	10	1 ml/kg 1 hr,3 times	Local irritation, 40% mortality	5
"	"	10	1 ml/kg 1 hr	Local irritation, 20% mortality	5

TABLE V-3 (continued)

Route	Animal	No.	Exposure	Observations	References Cited
Dermal	Rabbit	10	0.5 ml/kg 1 hr	Local irritation, no deaths	5
Intravenous	Cat	-	0.08 ml/kg	Minimum lethal dose	5
"	"	3	0.008 ml/kg	Transitory fall in blood pressure	5
"	Mouse, rat, guinea pig, and rabbit	-	0.10-0.14 ml/kg	LD50	12

Adapted from NIOSH Criteria for a Recommended Standard--Occupational Exposure to Epichlorohydrin (1) the 12th week four of the five rats developed spermatoceles, which were thought to render the rats permanently sterile.

The effects of repeated exposure to epichlorohydrin in animals are summarized in Table V-4 (1).

Occupational exposure to epichlorohydrin occurs chiefly by inhalation and skin contact and, to a limited extent, by ingestion (1). The effects of exposure to epichlorohydrin in humans which were summarized in the NIOSH criteria document (1) are tabulated in Table V-5. Eye and nose irritation, lung edema, kidney lesions, and changes in the voltage of the peaks of the alpha rhythm in EEG measurements have been observed in exposed humans.

The ACGIH has adopted a Threshold Limit Value (TLV) of 5 ppm (19 mg/m^3) for epichlorohydrin (G11).

2.5 Carcinogenicity

Van Duuren et al. (24) reported that epichlorohydrin given by subcutaneous injection was carcinogenic in mice. Fifty mice received weekly injections of 1 mg of epichlorohydrin in 0.1 ml tricaprylin for 26 weeks. The first sarcoma was noted after 126 days and the second one after 300 days (24). In a similar study, of 50 mice given weekly subcutaneous injections of 1 mg epichlorohydrin in 0.05 ml tricaprylin for 580 days, 6 were reported to have developed local sarcomas and 1 a local adenocarcinoma (25). Only 1 of 50 tricaprylin-treated controls was reported to have developed a local sarcoma.

Weil et al.(26) painted one "brushful" of undiluted epichlorohydrin on the clipped dorsal skin of 40 mice, thrice

TABLE V-4

EFFECTS OF REPEATED EXPOSURE TO EPICHLOROHYDRIN IN ANIMALS

Route	Animal	No.	Exposure	Observations	Reference Cited
Inhalation	Mouse	10	2,370 ppm 1 hr/day, up to 16 days (until all died)	Nose and eye irritation followed by gradual cyanosis, muscular relaxation of the extremities, stiffening of the tail, and fine body tremor; respiration decreased before death and ceased completely before cardiac arrest; terminal clonic convulsions in some animals	5
"	Rat	8	120 ppm 6 hr/day 5 days/wk 11 exposures (epichlorohydrin in propanol solution)	Labored breathing, profuse nasal discharge, weight loss, leukocytosis, increased urinary protein excretion (suggesting damage to kidney), and peripheral atrophy of cortical tubules (in 4 rats); lung congestion, edema, consolidation, and inflamed areas with signs of abscess formation; no effects from the propanol vehicle alone reported	16
"	"	8	56 ppm, 6 hr/day 5 days/wk 18 exposures	Respiratory distress, nasal discharge, weight loss	16
"	"	8	27 ppm, 6 hr/day 5 days/wk 18 exposures	Mild nasal irritation; hemorrhagic and consolidated areas in the lungs of one rat	16
"	"	8	17 ppm, 6 hr/day 5 days/wk 19 exposures	No effects	16

TABLE V-4 (continued)

Route	Animal	No.	Exposure	Observations	Reference Cited
Inhalation	Rat	8	9 ppm, 6 hr/day 5 days/wk 18 exposures	Pulmonary infection in two rats	16
"	"	15	5.2 ppm 24 hr/day 98 days	More leukocytes with altered fluorescence, increased urine coproporphyrin, kidney and lung damage, decrease in blood nucleic acid	17
"	"	15	0.5 ppm 24 hr/day 98 days	Increased modified leukocytes, reduced blood nucleic acid	17
"	"	15	0.05 ppm 24 hr/day 98 days	No effects	17
"	"	10	5.2-15.6 ppm 3 hr/day for 6.5 mo	No deaths or signs of intoxication; low body weight gain	18
Oral	"	-	15 mg/kg/day for 12 days	Infertility in male rats within 7 days, reversed when exposure discontinued for approximately 1 wk; testes, epididymides, prostate, and seminal vesicles examined histopathologically on the 12th day no different from those of untreated controls	14

Adapted from NIOSH Criteria for a Recommended Standard--Occupational Exposure to Epichlorohydrin (1)

TABLE V-5

EFFECTS OF EPICHLOROHYDRIN ON HUMANS (1)

Subject and Exposure	Observations	Comments	Reference Cited
39-year-old worker exposed to "a gust"	Eye and throat irritation followed by facial swelling, nausea, vomiting, headache, and dyspnea; enlarged liver, slight jaundice, and elevated serum bilirubin the next day; less jaundice after 18 days but liver still enlarged after 2 yr with altered function; bronchitic alterations in right lung 5 mo after exposure	Author concluded that liver damage and asthma-like bronchitis were results of epichlorohydrin exposure, but NIOSH suggested that liver damage could have had another cause and that conclusions about chronic effects could not be drawn from study.	19
53-year-old worker exposed to fumes for 30 min	Complaints of burning nose and throat, cough, and chest congestion several hours after exposure; also running nose, eye tenderness, and headache followed by nausea; symptoms gone within 3-4 days although subsequent complaints of more frequent respiratory infections	Report indicated the hazards associated with acute exposures to high concentrations, but according to NIOSH no quantitative conclusions could be made.	20
5 male workers, aged 19-32, dermally exposed	Severe redness, swelling, and red papules on exposed skin; in one worker, red skin discoloration and erythema for more than 2 mo; severe skin erosion and enlarged lymph nodes in another	Authors noted a latent period of several minutes to several hours before onset of symptoms and a direct relationship between intensity of burns and duration and extent of exposure.	13

TABLE V-5 (continued)

Subject and Exposure	Observations	Comments	Reference Cited
Four volunteers in an experiment on ocular light sensitivity exposed at 0.2-0.75 mg/m^3 (about 0.05-0.19 ppm)	No significant ocular changes	-	17
Accidental 1-hr occupational exposure to epichlorohydrin at 20 and 40 ppm	Transient burning of eyes and nasal passages in lower concentration; at higher level, eye and throat irritation lasting 48 hr	Concentration of 100 ppm suggested as intolerable for even a short period; method of measuring epichlorohydrin concentrations not reported.	21
Study of 48 employees exposed at least once to epichlorohydrin for periods of 7 days to 13 yr	Decreased percentage of polymorphonuclear leukocytes and increased percentage of monocytes in total leukocyte count in the blood	NIOSH considered the observed persistent changes not attributable solely to epichlorohydrin exposure and suggested that a detailed study of medical histories of individuals and their possible exposure to other chemicals was necessary for evaluation.	22
Retrospective epidemiological study based on medical examination data for 507 Dow Chemical Co. employees exposed to epichlorohydrin at unknown concentrations for at least 6 mo	Blood chemistry and liver and kidney functions in exposed individuals similar to company laboratory normal values	According to NIOSH, the study was inadequate because it lacked a control group, its estimates of exposure were "crude," and it did not consider individuals who dropped out because of illness, retirement, or death.	23

TABLE V-5 (continued)

Subject and Exposure	Observations	Comments	Reference Cited
Inhalation of epichlorohydrin at 0.05 and 0.08 ppm by five volunteers	Statistically significant changes in electroencephalographic (EEG) recordings at 0.08 ppm (the olfactory threshhold); no effects observed at 0.05 ppm	Because the exposure period was unspecified, the total dose is impossible to estimate.	17

weekly, for life. Thirty mice were still alive after 17 months; the last one died after 25 months. No tumors were observed.

Van Duuren et al. (25) found no tumors in 50 female mice that received 2 mg epichlorohydrin in 0.1 ml acetone on their clipped dorsal skin, three times/week, for 580 days. The median survival time was 506 days. However, 9 skin papillomas were noted in 30 mice given single skin applications of 2 mg epichlorohydrin in 0.1 ml acetone followed by thrice weekly skin applications of phorbol myristate acetate in acetone. Of 30 control mice receiving only the phorbol myristate acetate applications, 3 were reported to have developed papillomas. No tumors were found in acetone-treated controls (25).

Van Duuren et al. (25) also reported that weekly intraperitoneal injections of 1.0 mg epichlorohydrin in 0.05 ml tricaprylin produced papillary lung tumors in 11 out of 30 mice. No tumors were observed in the tricaprylin controls.

Kotin and Falk (27, as reported in 1) gave 30 mice epichlorohydrin (5 μM) in single subcutaneous doses and observed them for about 2 years. They reported finding a skin papilloma in one mouse after 11.5 months, a hepatoma in another after 13 months, and two lung adenomas in a third after 24 months. Except for the skin papilloma, the tumors were said to have been similar in type and frequency to those in the control group.

2.6 Mutagenicity

According to an EPA study, epichlorohydrin induced chromosome aberrations in bone marrow cells of female mice treated in vivo (28, as reported in G41). A dose response was said to have been observed 24 hours after single intraperitoneal administrations of 1-20 mg/kg and after oral administration of 5 or 20 mg/kg in single doses. Neither the number of animals nor the statistical analysis was included in the EPA report.

The EPA study also referred to a report by Kucerova (29, as reported in G41) that the leukocytes of workers exposed to epichlorohydrin for 1 year showed chromosome aberrations, but it considered the data presented by this study to be insufficient for evaluation. The blood samples were pooled, and the number of blood cells per worker and the number of workers analyzed were not reported.

Sram et al. (28, as reported in G41) were reported to have shown epichlorohydrin to be mutagenic in host-mediated assay tests with the *Salmonella typhimurium* strains G-46, TA 100, and TA 1950 in female mice given injections of epichlorohydrin at 50 and 100 mg/kg. They found a dose-response relationship in the induction of reversions to histidine prototrophy in the G-46 and TA 100 strains after the host mice were given single intramuscular injections and in the TA 1950 strain after single subcutaneous injections.

Elmore et al. (30, as reported in G41) incorporated epichlorohydrin in agar containing *S. typhimurium* TA 100 and reported that it produced dose-related reversions to histidine prototrophy over a range of 25.6-500 μM.

Epichlorohydrin was reported to have induced reversions to tryptophan prototrophy when 0.6 ml of a 1:1 ethanol solution of epichlorohydrin was added to a buffered suspension of 7 x 10^8 *E. coli* B/r (try-) (31, as reported in G41).

In a study by Koelmark and Giles (32, as reported in G41) epichlorohydrin was reported to have induced reversions to adenine prototrophy in Neurospora crassa W.40 "distinctus" A. The reported mutation frequency was 135.2 revertants per million survivors 1 hour after treatment of 73.6 million conidia with epichlorohydrin at 0.15 M in water.

An EPA report (G41) stated that epichlorohydrin induced chromosome aberrations in root tip meristems of Vicia faba and mutations at the eceriferum loci in barley but gave no experimental details.

Epstein et al. (33, as reported in G9) reported no dominant lethal mutations in mice given epichlorohydrin intraperitoneally at 150 mg/kg.

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

Jones et al. (34) stated that in rats epichlorohydrin yielded the same urinary metabolites as alpha-chlorohydrin (3-chloropropane-1,2-diol). The investigators found that when alpha-chlorohydrin was administered intraperitoneally or orally at 50 mg/kg, 2,3-dihydroxypropyl-S-cysteine and the corresponding N-acetate were excreted in the urine along with the unchanged compound. They concluded that epichlorohydrin was converted to alpha-chlorohydrin by hydrolysis of the epoxide ring.

2.9 Environmental Release and Ecological Effects

Most of the epichlorohydrin produced in 1974 was used as an intermediate in the production of glycerine, polymers, and a variety of other chemicals. Although only a small percentage of the amount of the chemical produced is expected to be lost during production or processing, the total released to the atmosphere might be of concern due to its high vapor pressure (12.5 mm at 20°C (G22)) and the large amount produced annually.

Air concentrations monitored in 1974 and 1975 in a Dow Chemical Company plant were in the range of 0.01-0.66 ppm in a unit producing epoxy resin and glycerine (35, as reported in 1).

Environmental monitoring within Russian plants producing epichlorohydrin and dichlorohydrin-glycerine showed epichlorohydrin at about 20 mg/m^3 (5.2 ppm) where employees withdrew quality control samples and at about 3.5 ppm during filling of tanks with epichlorohydrin (36, as reported in 1). In another Russian plant that discharged epichlorohydrin to the atmosphere, the maximum permissible concentration of 0.2 mg/m^3 was exceeded by 2.5-6 times, and 400 meters from the plant the permissible limit was exceeded in 5 of 29 samples analyzed. No epichlorohydrin was detected 500-600 meters from the plant (17, as reported in 1).

Epichlorohydrin has an Aquatic Toxicity Rating (96-hour TLm, species unspecified) of 100-10 ppm (G16).

No reports of ecological damage caused by the chemical were found.

2.10 Current Testing

G.J. Van Esch is conducting carcinogenicity studies with rats given epichlorohydrin orally at Rijks Instituut voor de Volksgezondheid, Netherlands (G13). According to Tox-Tips, K. Olson will be studying the effects of epichlorohydrin on fetal rats and rabbits at Dow Chemical Company, Midland, Michigan (37). Separate groups of Sprague-Dawley rats and New Zealand white rabbits will be exposed to epichlorohydrin at 0, 5, and 15 ppm in closed inhalation chambers for 6 hours/day on days 16-18 of the gestation period. All animals will be killed immediately before term, and fetuses will be examined morphologically and histopathologically.

Epichlorohydrin (NCI #C07001) has been tentatively selected by NCI for carcinogenicity studies in hamsters, mice, and rats exposed by inhalation (G12).

According to an abstract reported in the CANCERPROJ database, the Preventive Medicine and Community Health Department of the University of Texas School of Medicine at Galveston will conduct epidemiologic studies of employees of the Texas Division of Dow Chemical Company involved in the manufacture of epichlorohydrin (38).

1,1,1-TRICHLORO-2,3-EPOXYPROPANE (TCPO)

2.1 Bioaccumulation

No information was found in the sources searched.

2.2 Impurities and Environmental Degradation or Conversion Products

No information was found in the sources searched.

2.3 Acute Toxicity

No information was found in the sources searched.

2.4 Other Toxic Effects

TCPO has been characterized as an enzyme inhibitor. Extensive studies have been performed to evaluate its effect on the pathobiological processes of various toxic substances.

Oesch (39) has reviewed the literature on mammalian epoxide hydrases, inducible enzymes that catalyze the inactivation of some carcinogenic and cytotoxic metabolites. TCPO was reported to be the most potent inhibitor of epoxide hydrase. With ^{3}H-styrene oxide as a substrate, TCPO inhibited epoxide hydrase prepared from guinea pig liver. TCPO at one-fifth the substrate concentration completely inhibited the hydration. Seidegard et al. (40) reported a similar uncompetitive inhibition of epoxide hydrase prepared from the rat lung.

Van Duuren and Banerjee (41) demonstrated that the binding of trichloroethylene (TCE) metabolites to rat hepatic microsomal protein was increased by 13-91% in the presence of TCPO. The authors suggested that the covalent binding was via an epoxide or other related electrophilic species.

Kappus et al. (42) demonstrated that TCPO did not affect the uptake of vinyl chloride by rat liver microsomes but, in its presence, the irreversible binding of vinyl chloride metabolites to microsomal protein was increased twofold.

Alexandrov and Thompson (43) reported that TCPO (5×10^{-3}M) inhibited aryl hydrocarbon hydroxylase activity in vitro but increased the binding of benzo(a)pyrene (BP) to liver nuclei preparations from male rats pretreated with either phenobarbitol or methylcholanthrene (MCA) and from untreated male rats. TCPO in the incubation mixture was also reported to selectively inhibit metabolism by preventing the formation of diols, phenols, and to a lesser degree quinones.

In experiments reported by Berry et al. (44), TCPO slightly enhanced the enzymatic covalent binding of MCA and BP to DNA in epidermal homogenates in vitro but did not have a similar effect on 9,10-dimethyl-1,2-anthracene (DMBA) or dibenz(a,h)-anthracene (DBA). TCPO also was reported to have increased the tumorigenic effects of BP and MCA in mice, perhaps by inhibiting hydration, and to have decreased the tumor latency period for BP and MCA exposure.

Bürki et al. (45) studied the effect of TCPO on the carcinogenic potential of MCA. In two separate experiments, TCPO (1.5 μmoles), MCA (1.5-3 μmoles), and MCA plus TCPO were applied topically to the backs of 10-week-old mice, twice a week, for 3 weeks or for 17 weeks. With either exposure period, 87% of the mice that received only MCA developed tumors, whereas 100% of those exposed to the combined substances developed tumors. Both the total number of tumors and the rate at which they appeared were significantly higher in mice exposed to MCA plus TCPO than in those exposed to MCA only. Only 1 tumor was detected in 56 mice exposed to TCPO. The authors suggested that TCPO increased the carcinogenic effect of MCA by inhibiting hydration, which increased the cellular concentration of MCA or its metabolites.

2.5 Carcinogenicity

Topical application of TCPO at doses of 1.5 μmoles for 3 or 17 weeks did not induce tumors in mice, according to a study by Bürki et al. (45). However, it did enhance the tumorigenic effects of MCA. See 1,1,1-Trichloro-2,3-Epoxypropane (TCPO), Section 2.4.

2.6 Mutagenicity

No information on the mutagenicity of this compound was found in the sources searched.

2.7 Teratogenicity

Injecting pregnant mice subcutaneously with TCPO on day 11 of gestation was reported to have induced no orofacial anomalies (46). However, the injected mice had 6.7% resorption of implantations, whereas untreated mice had 1.9%.

2.8 Metabolic Information

No information was found in the sources searched.

2.9 Environmental Release and Ecological Effects

No information was found in the sources searched.

2.10 Current Testing

The effect of TCPO on the activation of aflatoxin B1 to metabolites that are mutagenic in Neurospora is being studied at the National Institute of Environmental Health Sciences, Research Triangle Park, N.C. T. Ong and J. Guthrie are the principal investigators (38).

At the University of Tennessee, D. Berry and T. Slaga are using TCPO to study the role of the aryl hydrocarbon hydroxylase in mouse skin tumorigenesis by benz(a)pyrene and 7,12-dimethylbenz(a)anthracene (DMBA) (38).

2.1 Bioaccumulation

No information was found in the sources searched.

2.2 Impurities and Environmental Degradation or Conversion Products

No information was found in the sources searched.

2.3 Acute Toxicity

No information was found in the sources searched.

2.4 Other Toxic Effects

No information was found in the sources searched.

2.5 Carcinogenicity

No tumors were observed when 100 mg of a 10% solution of epibromohydrin in acetone was painted on the dorsal skin of 30 mice, 3 times a week, for up to 544 days (47).

2.6 Mutagenicity

Epibromohydrin was shown to induce reverse mutations in the purple adenineless mutant (38701) of *Neurospora crassa* W. 40 "distinctus" (32). Epibromohydrin at a 0.08 molar concentration induced 2.8 reverse mutations per million viable cells and 7.2 per million surviving cells. The overall survival rate was 39.3%.

Epibromohydrin has also been tested for mutagenicity with a *Klebsiella pneumoniae* auxotroph, but the results cannot be determined from the report of the test (8).

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

No information was found in the sources searched.

2.9 Environmental Release and Ecological Effects

No information was found in the sources searched.

2.10 Current Testing

No information was found in the sources searched.

1,4-DICHLORO-2,3-EPOXYBUTANE

No information about the biological properties of 1,4-dichloro-2,3-epoxybutane was found in the sources searched.

2.1 Bioaccumulation

No information was found in the sources searched.

2.2 Impurities and Environmental Degradation or Conversion Products

The constituents of technical grade 1,1,1-trichloro-3,4-epoxybutane (TCBO), as listed by the manufacturer Olin Chemicals (4), are given in Table V-6.

TABLE V-6

CONSTITUENTS OF TECHNICAL GRADE TCBO

Constituent	Percentage
TCBO	70 ± 3 (GLC)
Impurities in production material	
Tetrachlorobutyl alcohol, maximum	4
Dichlorobutylene-3,4-epoxide, maximum	5
Carbon tetrachloride, maximum	5
Higher molecular weight derivatives of the compound (mainly tetrachlorobutyl alcohol)	16
Chlorine content	60.5
Water	0.8

The compound's boiling point is 174°C, but it decomposes at 155°C, with HCl being liberated (3).

2.3 Acute Toxicity

The oral LD50 for TCBO in rats is 1.5 g/kg (2). Its dermal LD50 in rabbits ranges between 0.2 and 2.0 g/kg. The compound is a severe skin irritant and an eye irritant in rabbits. It was reported to be nontoxic to rats exposed at 200 mg/liter for 1 hour (2,3).

2.4 Other Toxic Effects

No information was found in the sources searched.

2.5 Carcinogenicity

No information was found in the sources searched.

2.6 Mutagenicity

Although no experimental details were provided, TCBO was reported to have given positive results in the Ames microbial mutagenic test (2,3).

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

No information was found in the sources searched.

2.9 Environmental Release and Ecological Effects

No information was found in the sources searched.

2.10 Current Testing

No information was found in the sources searched.

TETRAFLUOROETHYLENE EPOXIDE (TFEO)

No information about the biological properties of tetrafluoroethylene epoxide was found in the sources searched.

HEXAFLUOROPROPYLENE EPOXIDE (HFPO)

No information about the biological properties of hexafluoropropylene epoxide was found in the sources searched.

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POLYCHLORINATED TERPHENYLS

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POLYCHLORINATED TERPHENYLS

AN OVERVIEW

Polychlorinated terphenyls (PCT's) are complex mixtures of terphenyls with different numbers and arrangements of chlorine atoms. When pure, they are white crystalline solids, but in commercial grades they are light yellow. Commercial mixtures are numbered according to the percentage of chlorine in them. In the Aroclor series, for example, the last two digits in the number denote the percentage of chlorine. Commercial PCT's contain polychlorinated biphenyls (PCB's) as impurities.

PCT's are produced by chlorination of commercial terphenyl, which itself is usually a mixture of ortho-, meta-, and par terphenyls. In the United States, a reported 8.1 million pounds were produced in 1972. However, the manufacturer discontinued their production in that year, because concern had arisen over the environmental effects of the chemically similar PCB's and because all their uses were dispersive. Since then, PCT's have been imported in small but increasing quantities--from 160,000 pounds in 1973 to 400,000 pounds in 1975.

Before 1973, PCT's were used primarily as plasticizers and in adhesives, inks, sealants, caulking compounds, and waxes. They are now used mainly in waxes for investment casting, an application that leads to their release into the environment.

No information on the occupational or general population exposure to PCT's was found in the sources searched.

PCT's have been detected in cheeses, fish, oysters, and human tissues in various locations around the world. No adequate information on the ecological effects of these chemicals was found in the sources searched. They are expected to be very stable; only the lower chlorinated homologs are likely to be degraded at a significant rate by hydrolytic or similar reactions under normal environmental conditions.

Erosion of gastric mucosa, alopecia, facial and pericardial edema, and eye discharge were observed in rhesus monkeys fed PCT's. PCT's are also inducers of hepatic microsomal enzymes. Information on their potential for carcinogenicity, mutagenicity, or teratogenicity could not be located in the sources searched.

POLYCHLORINATED TERPHENYLS

PART I

GENERAL INFORMATION

1.1 Identification

CAS No.: 061788338
NIOSH No.: TQ13800

1.2 Synonyms and Trade Names

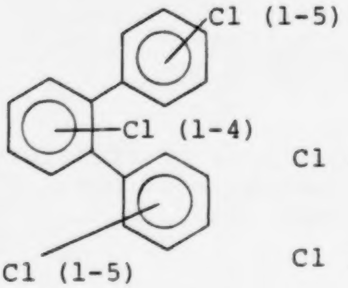
Polychlorinated triphenyls; polychlorinated diphenylbenzenes; PCT's; Aroclor 54xx (Monsanto, production discontinued); Electrophenyl T-xx(Prodelec); Kanechlor KC-C-xx(Kanegafuchi)

(1)

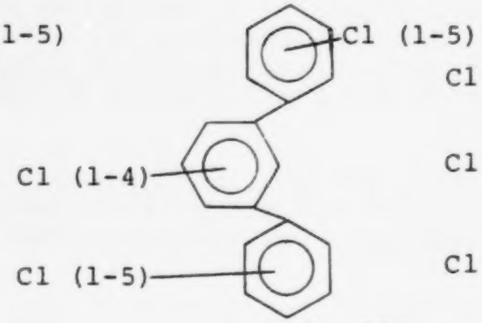
1.3 Chemical Formula and Molecular Weight

$C_{18}H_{14-n}Cl_n$

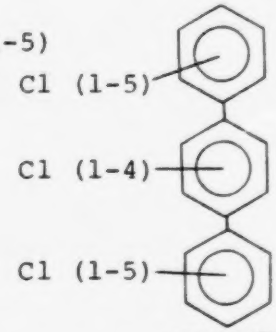
Mol. wt. 437 (n=6)
575 (n=10)



ortho-PCT



meta-PCT



para-PCT

(G17)

1.4 Chemical and Physical Properties

1.4.1 Description: Polychlorinated terphenyls are produced by chlorination of commercial terphenyl (a mixture of ortho-, meta-, and para-terphenyls). As commercial products, they are mixtures of chloroterphenyls, with varying numbers of chlorine atoms (homologs) and varying molecular arrangements (isomers). They are differentiated by the percentage of chlorine in the mixture.

1.4.2 Boiling Point: See Section 1.8, Table VI-1.

1.4.3 Melting Point: See Section 1.8, Table VI-1.

1.5 Production and Use

1.5.1 Production:

1968	(domestic)	8.9 million lb
1969	(domestic)	11.6 million lb
1970	(domestic)	17.8 million lb
1971	(domestic)	20.2 million lb
1972	(domestic)	8.1 million lb
1973	(imports)	ca. 160,000 lb
1974	(imports)	330,000 lb
1975	(imports)	400,000 lb

Note: Imports may increase as polychlorinated terphenyls replace decachlorobiphenyl in investment casting.

(4)

1.5.2 Use: Now primarily in waxes for investment casting (lost-wax process). In 1975, four major wax manufacturing companies supplied 135 investment casting foundries in the U.S.

(4)

Prior to 1974, used primarily as plasticizers (mostly Aroclor 5460) in adhesives, inks, sealants, caulking compounds, and waxes

(4)

1.6 Exposure Estimates

1.6.1 Release Rate: Current use primarily environmentally dispersive; although wax is reused, at least 5-10% deliberately discarded after each casting

(4)

1.6.2 NOHS Occupational Exposure:

No information was found in the sources searched.

1.7 Manufacturers

Monsanto ceased production of polychlorinated terphenyls in 1972 because of their similarities to PCB's and because they had no closed uses. PCT's as well as PCB's were marketed under the trade name "Aroclor". Most imported PCT's come from France, where they are manufactured by Prodelec. The major importers are Progil, Inc., and Instel, Co.

(2,4)

1.8 Data on Specific Polychlorinated Terphenyls

See Table VI-1.

TABLE VI-1

CHARACTERISTICS OF COMMERCIAL MIXTURES (2,3,G17)

Name	Description	CAS No.	NIOSH No.	Chlorine Content	Distillation Range	Softening Point
Aroclor 5442*	Clear, yellow, sticky resin	012642238	TQ13850	42%	215-300°C	46-52°C
Aroclor 5460*	Clear, yellow to amber brittle resin	011126424	TQ13900	60%	280-335°C	98-105.5°C
Electrophenyl T-60**	-	-	-	60%	-	-

*Production terminated by Monsanto
**Produced by Prodelec, France (1)

Note: Aroclor numbers starting with 54 refer to PCT's and those starting with 44 or 25 refer to mixtures of PCT's and PCB's. The last two digits in the number indicate the percentage of chlorine by weight in the mixture (1).

POLYCHLORINATED TERPHENYLS

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

The similarity of PCT's to PCB's--both are chemically unreactive and have low water solubility--indicates that PCT's have a potential for bioaccumulation.

PCT's persisted in cod tissues for at least 70 days after one-time oral dosage (see Section 2.2) and were detected in eggs and fatty tissues of herring gulls (*Larus artentatus*) from the Bay of Fundy. PCT's were also found, and presumably were stored, in human tissues (see Section 2.9).

2.2 Impurities and Environmental Degradation or Conversion Products

Commercial PCT's are mixtures that vary in composition and degree of chlorination and possibly according to batch (G16). Aroclor series 25 and 44 contain mixtures of PCB's and PCT's; series 54 was reported to contain only PCT (5). In addition, terphenyl compounds can exist in three isomeric forms (ortho, meta, and para). Separation and identification of the three isomers is difficult because hundreds of PCT isomers are theoretically possible and few have been characterized. PCT's are known to contain PCB's as impurities (4).

According to a 1976 WHO monograph (1), PCT's are stable in the environment. Chemically, the PCT's, like the PCB's (1), are expected to be very stable and only the least chlorinated homologs are likely to be degraded at a significant rate by hydrolytic or similar reactions under environmental conditions.

Addison et al. (6) noted a reduction of the lower chlorinated PCT's in the excretions of cod (Gadus morhua) dosed orally one time with Aroclor 5460. This effect, also obtained with PCB's, was ascribed to preferential absorption of the isomers with lower chlorine contents. The authors reported further that the efficiency of absorption and excretion of PCT's in the cod seemed poor and that PCT's were found in all tissues analyzed, with the highest concentrations in the liver. Appreciable amounts of PCT's were found in the tissues 70 days after exposure, indicating their persistence.

Although no specific information on the degradation products of PCT's was found in the sources searched, they can be expected, because of their similarity to PCB's, to be excreted as phenolic metabolites and to appear unchanged in milk. In birds, PCT's can be expected to be excreted in eggs (5,1).

2.3 Acute Toxicity

The acute toxicity of PCT's, as reported by Fishbein (7), is given in Table VI-2.

TABLE VI-2

ACUTE TOXICITY OF PCT's

Compound	Parameter	Dosage	Animal	Route
Aroclor 5442	LD50	10,600 mg/kg*	Rat	Oral
"	MLD	>1,260<2,000 mg/kg*	Rabbit	Skin
Aroclor 5460	LD50	>19,200 mg/kg**	Rat	Oral
"	MLD	>7,940 mg/kg**	Rabbit	Skin

*Administered orally as 50% solution in corn oil
**Administered orally as 33.3% solution in corn oil

2.4 Other Toxic Effects

WHO reported (1) that there had not been any systematic studies on the toxicity of the PCT's.

Sosa-Lucero and de la Iglesia (8) studied the effects of Aroclor 5460 on liver microsomal systems and the distribution of the compound in rats. Residues were found in the blood, brain, testis, kidney, spleen, heart, fat, and liver in groups of six male rats who had been fed ad libitum a diet containing the compound at 10, 100, and 1,000 ppm in their diet for 7 consecutive days. No residues were found in the control group. Increases in drug-metabolizing enzyme activities and in the content of microsomal protein, phospholipids, and cytochrome P-450 were reported. No adverse effects on health or body weight were noted, but significant liver enlargement was observed at 1,000 ppm.

Bitman et al. (9) assessed estrogenic activity by determining the stimulation of the glycogen response of the immature rat uterus 18 hours after administration of the test compound. Aroclor 5442 was reported to be active and Aroclor 5460 inactive.

Allen et al. (10) administered Aroclor 5460 at 5,000 ppm in the diet of six rhesus monkeys for 3 months. Within 1 month the animals had lost considerable hair. At the end of the experiment, five had an average weight loss of 19%. Acneform lesions of the skin, subcutaneous edema, ascites, pleural effusion, pericardial edema, liver hypertrophy, and gastric mucosal hypertrophy and hyperplasia were observed. Decreases in hepatic microsomal esterase, aniline hydroxylase, nitroreductase, and glucose-6-phosphatase specific activities per gram of microsomal protein were reported. N-Demethylase activity was increased. Hematological changes developed gradually over a period of 3 months. A decrease in hemoglobin of approximately 2 g/100 ml and a decrease in hematocrit from 40% to 33% occurred. No major modifications in the total white cell count were noted, but there was a gradual decrease in the number of lymphocytes and a concomitant increase in neutrophils. The total serum protein also decreased and the albumin/globulin ratio of the serum protein gradually shifted.

2.5 Carcinogenicity

No reports of long-term carcinogenicity studies with PCT's were found in the sources searched. Allen and Norback (11) fed Aroclor 5460 at 5,000 ppm to six rhesus monkeys for 3 months. The effects reported were hypertrophy, hyperplasia, and dysplasia of the gastric mucosa. The authors suggested that their findings indicated a potential for carcinogenicity and necessitated thorough testing.

2.6 Mutagenicity

No information was found in the sources searched.

2.7 Teratogenicity

No information was found in the sources searched.

2.8 Metabolic Information

No information was found in the sources searched.

2.9 Environmental Release and Ecological Effects

In 96-hour static bioassays with bluegills and channel catfish exposed to Aroclors 5432, 5442, and 5460, only a few fish were killed even by exposure at 100 ppm (12).

Zitko et al. (5) found PCT's at 1.4 and 0.1 ppm in the subcutaneous fat and eggs of Canadian herring gulls (*Larus argentatus*), respectively. Thomas and Reynold (13) found

PCT's at 0-163 ppm in paperboard samples used in food packaging. In the Netherlands, Freudenthal and Greve (14) found PCT's at 0.07 ppb in water from the Rhine River, at 0.12 ppm in oyster tissue, at 0.4 ppm in eel fat, and at 0.5 ppm in human fat.

There are a number of additional reports on the presence of PCT's in human tissues. According to Doguchi and Fukano (15), the average concentration of PCT's in the blood of 27 Tokyo residents, none of whom had any known contact with the chemicals, was 5 ppb. This concentration was greater than the 3.2 ppb of PCB's in the same blood samples, even though far more PCB's (58,000 tons) than PCT's (2,000-3,000 tons) had been used in Japanese industry up to 1971.

Doguchi et al. (16) found PCT's at 0.1-2.1 ppm, with an average of 0.6 ppm, in the fat of 20 Tokyo residents. In most of the reports, residues were confirmed by perchlorination to give peaks of the perchloroterphenyls or by gas chromatography/mass spectrometry.

Takizawa and Minagawa (17), as reported by WHO (1), found the following amounts of PCT's (in ppm) in human tissues: liver (0.02), kidney (0.01), brain (0.02), and pancreas (0.04). Nishimoto et al. (18), according to Doguchi and Fukano (15), have identified PCT residues in human fat and milk and in samples of water and sludge. Minagawa et al. (19) reported residues of PCT at 0.37 and 0.012 ppm on a fat weight basis in human omentum major and breast milk. Whether these residues present a hazard to humans or to the environment has not been established.

Yap et al. (20) reported that Aroclor 5460 inhibited the in vitro activity of fish ATPases. PCT inhibited Mg^{2+}-ATPase from the muscle of bluegill fish by 31.9% at 0.03 ppm and by 42.9% at 0.33 ppm. This enzyme and NA^{+}-K^{+}-ATPase from the brain, liver, and kidney were also inhibited by concentrations of PCT in the 0.0310 ppm range.

2.10 Current Testing

No information was found in the sources searched.

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PYRIDINE

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PYRIDINE

AN OVERVIEW

Pyridine is a colorless or slightly yellow liquid with a disagreeable odor. It is miscible with water, oils, ethanol, diethyl ether, petroleum ether, and many other organic liquids. Pyridine is volatile with steam. The technical product composition of pyridine is usually reported as a distillation range.

Pyridine can be derived from coal carbonization and can be recovered from coke-oven gases and from coal tar middle oil. It can be synthesized from acetaldehyde and ammonia. The production of pyridine in the United States exceeded 60 million pounds in 1976.

Pyridine has been exported to the United Kingdom (33% of U.S. output in 1970) for the production of the herbicides diquat and paraquat. It is also used as a solvent and reagent in the manufacture of antihistamines, anti-infectives, piperidine, and waterproofing agents in the textile industry, and in miscellaneous compounds such as flavoring agents.

No information on the release rate of pyridine was found. According to the NOHS, 249,000 persons are estimated to have occupational exposure to pyridine. SRI estimated the U.S. human oral exposure to pyridine at 5.04×10^5 g/year, primarily resulting from its presence in food.

Pyridine is often found in municipal waste water and has been reported to be present in the working area

around coal furnaces and in agricultural crops and fish. The compound was reported to have inhibited cell multiplication in the bacterium *Pseudomonas putida* and the alga *Microcystis aeruginosa*. Pyridine also showed the potential for chronic toxicity in *Daphnia magna*.

Toxic effects attributed to pyridine in animals and humans have been reported in the literature. It causes central nervous system depression and irritation of the skin and respiratory tract. Large doses produce gastrointestinal disturbances and liver damage. Data from long-term tests on pyridine are inadequate for evaluation of its chronic effects, including carcinogenicity. No reports of relevant tests for mutagenicity or other short-term tests were found. The only article found on the teratogenic effects of pyridine reported that it caused abnormalities in chicken embryos. The metabolic fate of most of an administered dose of pyridine is unknown, but hydroxylation, N-methylation, oxidation, and conjugation reactions have been reported.

PYRIDINE

PART I

GENERAL INFORMATION

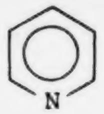
1.1 Identification

CAS No.: 000110861
NIOSH No.: UR84000

1.2 Synonyms and Trade Names

Azabenzene; azine (G16)

1.3 Chemical Formula and Molecular Weight



C_5H_5N Mol. wt. 79.10

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Flammable, slightly yellow or colorless liquid with nauseating odor and burning taste (G21)

1.4.2 Boiling Point: 113-115°C (1)

1.4.3 Melting Point: -42°C (G22)

1.4.4 Absorption Spectrometry:

$$\lambda_{max}^{cyclohexane} = 251, 256, 279, 284, 288 \text{ nm}$$

$$\log \varepsilon = 3.1, 3.1, 2.0, 1.8, 1.4$$

(G22)

1.4.5 Vapor Pressure: 10 mm at 13.2°C (G22)

1.4.6 Solubility: Soluble in ligroin and fatty oils; soluble in all proportions in water, alcohol, ether, benzene, acetone, and chloroform (G21, G22)

1.4.7 Octanol/Water Partition Coefficient:

$\text{Log } P_{oct} = 1.04$ (G36)

1.5 Production and Use

1.5.1 Production:

>60 million lb (1976 capacity) (G15)

1.5.2 Use:

In the synthesis of vitamins and drugs; in waterproofing; as a rubber chemical; as a denaturant for alcohol and antifreeze mixtures; as a dyeing assistant in textiles; in fungicides; as a solvent for anhydrous mineral salts, in organic syntheses, and in analytical chemistry

(G21,G23)

Quantitative Distribution (1975 U.S. Consumption):	Percentage
Exports (primarily to U.K. for the production of the herbicides diaquat and paraquat)	50
Solvent and reagent uses	16
Manufacture of antihistamines and anti-infectives	13
Manufacture of piperidine	7
Manufacture of textile waterproofing agents	7
Miscellaneous uses, e.g., flavoring agent	7
	100

5.04×10^5 g/year estimated to be in food (1)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information was found in the sources searched.

1.6.2 NOHS Occupational Exposure:

Rank: 602

Estimated no. of persons exposed: 249,000*

*rough estimate (G29)

1.7 Manufacturers

Koppers Co., Inc.
Nepera Chemical Co., Inc. (G24)

PYRIDINE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

No information was found on the bioaccumulation of pyridine.

2.2 Impurities and Environmental Degradation or Conversion Products

Refined technical pyridine boils within a 2° range (113-115°C) (1). Small amounts of a technical product that is a mixture of alkylated pyridines are also sold (1). Pyridine is stable under reducing conditions, but it is readily oxidized. Because of its high vapor pressure (20 mm/25°C (G15)), it can be expected to volatilize to the atmosphere, where it may photo-oxidize.

2.3 Acute Toxicity

The acute toxicity of pyridine, as reported in the NIOSH Registry of Toxic Effects of Chemical Substances (G16), is given in Table VII-1.

TABLE VII-1
ACUTE TOXICITY OF PYRIDINE

Parameter	Dosage	Animal	Route
LD50	891 mg/kg	Rat	Oral
"	4,000 ppm/4 hr	"	Inhalation
"	1,000 mg/kg	"	Subcutaneous
"	880 mg/kg	Dog	Intravenous

TABLE VII-1 (Continued)

Parameter	Dosage	Animal	Route
LD50	1,121 mg/kg	Rabbit	Dermal
LDLo	4,000 mg/kg	Guinea pig	Oral
"	1,200 mg/kg	Mouse	Intraperitoneal
"	870 mg/kg	Guinea pig	"

Pyridine is pharmacologically active by its effect on the central nervous system (G38). It produces weakness of limbs, ataxia, unconsciousness and salivation by any route of administration (G1). Exposure to pyridine vapors produces moderate mucous membrane irritation (G38).

In anesthetized dogs, pyridine administered intravenously at a dose of 880 mg/kg of body weight (equivalent to the LD50) produced salivation, myosis, lacrimation, nasal secretion, micturition, cloudy cornea, apnea, and death by cardiac failure (2). Decreased blood pressure and marked tachycardia also occurred at this dose level.

Exposure of rats to pyridine vapors at 5-10 mg/liter for a single 40-minute period decreased the glutamine level in the kidneys and increased the ammonia excretion in the urine (3). No changes in ammonia or glutamine levels in the liver were observed.

2.4 Other Toxic Effects

Six rats given diets with 0.1% pyridine gradually lost weight and died in 2-4 weeks. Lesions of the liver and kidneys and cirrhosis of the liver were observed (4).

Baxter (5,6) hypothesized that pyridine might, by its methylation in the body, cause hepatic and renal injury by draining the labile methyl groups from choline and methionine, thus producing an "intrinsic" deficiency of these substances. Administration of pyridine (0.34-1.0%) to rats for up to 4 months in diets containing low levels of casein and choline appeared to induce necrosis and fatty changes in the liver. Rats given pyridine with more nearly optimal diets developed necrosis with vascular engorgement and hemorrhages in the central areas. Renal damage often occurred in animals with hepatic injury (5). Increasing the choline (and casein) content of the diet caused a marked reduction in fatty changes and fibrosis without any significant reduction in the severity and extent of the acute necrosis. Tumor-like nodules were observed in the livers of some rats. Parenchymal cells at the edges of old necrotic areas in the livers contained accumulations of oval cytoplasmic bodies that stained dark brown with hematoxylin and gave the histochemical reactions of calcium (calcification) (6).

Administration of pyridine intravenously to anesthetized dogs resulted in the following (2):

a) Increased serum glutamic-oxaloacetic transaminase (SGOT) and blood urea and decreased serum alkaline phosphatase, at doses of 88-380 mg/kg body weight. According to the authors these changes support the concept that pyridine in high and lethal doses causes liver and kidney damage.

b) Reduced blood pressure only at lethal doses, which according to the authors suggests that the effect on blood pressure is secondary to the primary action on the central nervous system.

Kondratyuk (7, from TOXLINE abstract) reported that rats ingesting pyridine at 0.2 mg/liter in drinking water containing calcium ions (100 mg/liter) showed a thickening of the mucous membrane folds of the stomach, abundant mucus in the stomach with small amounts in the duodenum, as well as catarrhal symptoms and ulcerations. Kondratyuk also indicated that calcium in drinking water increased the toxic effects of pyridine to a greater degree than magnesium.

Toxic effects of pyridine in humans have been reported. Small oral doses (2-3 ml) produced mild anorexia, nausea, fatigue, and mental depression (G26).

Most of the effects observed in humans exposed to pyridine are transient and occur in the central nervous system and gastrointestinal tract (G38). The symtoms include headache, dizziness or giddiness, nervousness, insomnia, mental dullness, nausea, and anorexia. In some cases, lower abdominal or back discomfort with frequent urination has been observed. These transient symptoms, without associated evidence of liver or kidney damage, have occurred in individuals exposed to pyridine vapors at an average concentration of 125 ppm, 4 hours a day, for 1-2 weeks.

Serious liver and kidney injury occurred in two individuals treated for epilepsy with pyridine in daily oral doses of 1.8-2.5 ml for up to 2 months (8). One of the treated individuals died. No toxic effects except heartburn and occasional nausea were reported in humans exposed to pyridine in oral doses of 0.31-1.54 ml (8).

Effects on the nervous system, including speech disorders, were observed in a 29-year-old woman who inhaled vapors from spilled pyridine for 15-20 minutes. No irritation of the upper respiratory tract was caused by this accident (9, from TOXLINE abstract).

2.5 Carcinogenicity

Pyridine was administered to rats (Fischer 344) by subcutaneous injection, twice a week, for 1 year at four dose levels (3, 10, 30, 100 mg/kg). The rats were held an additional 6 months for observation. Neither the total tumor incidence nor the incidence at particular sites were higher in the exposed animals than in controls (10).

Large tumor-like nodules in livers of some rats exposed to pyridine at 0.34-1.0% in the diet for up to 4 months have been reported (6). No evidence of invasion or metastases was seen.

Repeated subcutaneous injections of 5% pyridine produced epithelial proliferation in rabbit ears (11, as reported in G18). The strain or type of rabbit, the number of survivors, and the duration of the experiment were not given.

By current standards, none of these studies are considered adequate to judge the carcinogenicity of pyridine.

2.6 Mutagenicity

No information was found in the sources searched.

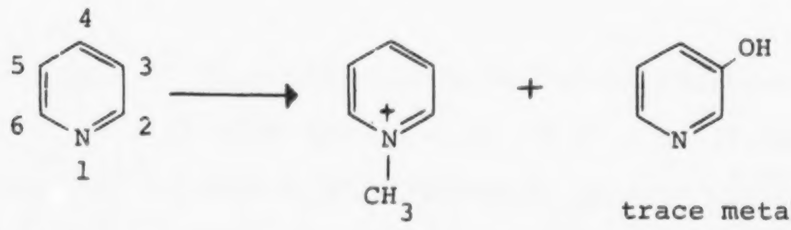
2.7 Teratogenicity

Developmental abnormalities were reported in chicken embryos as follows (12, from TOXLINE abstract):

"Pyridine (20 mg/egg) caused typical muscular hypoplasia of the legs and on rare occasions, abnormality of the facial skeleton and neck vertebrae. Pronounced synergistic effect was observed by the joint treatment with ethionine and pyridine."

2.8 Metabolic Information

The fate in the body of most of an administered dose of pyridine is unknown (13). Hydroxylation, N-methylation, oxidation, and conjugation reactions, however, have been identified (G38). In rabbits, oral treatment with pyridine (0.25 g/kg) did not disturb the ethereal sulphate or glucuronic acid output, although traces of 3-hydroxypyridine were excreted. N-Methylpyridinium ion and 3-hydroxypyridine (shown below) are reported metabolites of pyridine, but they accounted for only a small portion of the administered dose (13).



trace metabolite

Pyridine N-Methylpyridinium ion 3-Hydroxypyridine

Earlier reports (14) suggested that methylation is probably a detoxification reaction of pyridine. Pyridine is partly converted by most animals (except the rabbit) to N-methylpyridinium hydroxide.

When pyridine acetate was administered to dogs (route unspecified), methylpyridinium hydroxide equivalent to about 4% of the dose appeared in the urine (13). Methylation of the pyridine in the pig, goat, hen, and frog also has been reported. According to early investigations, rabbits did not methylate pyridine although they excreted some pyridine unchanged. A more recent article reported that a small amount (113 mg) of the methylated compound was isolated as the chloroplatinate ($(C_6H_7N,HCl)_2PtCl_4$) after rabbits were fed 15 g of pyridine. Pyridine is probably methylated in man; small quantities of the methylated compound occur in urine (13).

Pyridine also can be metabolized by N-oxidation, which represents a pathway of metabolic activation (G10). (The N-oxide is a more potent fungicide than the parent compound.)

2.9 Environmental Release and Ecological Effects

Data on the toxicity of pyridine in aquatic organisms is given in Table VII-2:

TABLE VII-2

ACUTE TOXICITY OF PYRIDINE IN AQUATIC ORGANISMS

Species	Parameter	Duration of Exposure	Concentration	Reference
Mosquito fish (*Gambusia affinis*)	TLm	96 hr	1,300 ppm	15
Water flea (*Daphnia magna*)	TLm	48 hr	944 mg/liter	17
Carp (*Cyprinus carpio*)	TLm	96 hr	26 ppm	18

The toxicity threshold concentration for long-term exposure in Daphnia magna was reported to be 40 mg/liter (19).

A secondary source (1) reported that Russian investigators (20,21) detected pyridine in the working area around coke furnaces and in agricultural crops and fish. A subsequent study (22, from TOXLINE abstract) indicated that pyridine and phenols were taken up by crops sprayed with 500 m^3/hectare of effluent water from coke manufacturing plants, whereas benzene and naphthalene in the waste water were not detected in plants. Pyridine has also been detected in four water supplies (23).

Pyridine at 340 mg/liter and 28 mg/liter was reported to inhibit cell multiplication in the bacterium Pseudomonas putida and the alga Microcystis aeruginosa, respectively (G40).

The nematode Caenorhabditis elegans showed a positive chemotactic response toward pyridine at 0.1-1 mM (16).

2.10 Current Testing

Pyridine has been approved for carcinogenicity bioassay by NCI (G12) because of large annual production, widespread use, high potential for human exposure, and the lack of adequate test data (1).

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1,1,1-TRICHLOROETHANE

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1,1,1-TRICHLOROETHANE

AN OVERVIEW

1,1,1-Trichloroethane, which is also known as methyl chloroform and alpha-trichloroethane, is a colorless liquid. It is insoluble in water but soluble in chloroform, alcohol, and ether. Commercial products contain small amounts of stabilizing material, such as para-dioxane and tetraethyl lead.

1,1,1-Trichloroethane can be produced by reaction of 1,1-dichloroethylene with hydrogen chloride in the presence of catalysts. U.S. production of this chemical in 1976 was 631 million pounds, reflecting a growth rate of about 9.5% per year since 1966, when 250 million pounds were produced. In 1974, U.S. imports are believed to have been negligible; exports are estimated to be 70 million pounds.

This compound is used as a cleaning solvent for metals and other materials. It also has miscellaneous uses, for example as an aerosol component, a coolant in metal cutting oils, and a carrier for lubricants.

According to NOHS, 2,904,000 workers in the United States are occupationally exposed to 1,1,1-trichloroethane, whereas a NIOSH criteria document estimated that 100,000 workers are potentially exposed to the compound. SRI International estimated that in 1972, when 440 million pounds of the compound were produced, 6.6 million pounds were lost to the environment during manufacturing and 278 million pounds were released to the environment in its commercial use pattern.

The compound's high volatility reduces its potential for bioaccumulation.

In view of the exponential growth in its production, 1,1,1-trichloroethane appears to pose a major threat to stratospheric ozone. (Among man-made chemicals, only Freon 11 and Freon 12 are considered to present more serious threats.) There is some concern that, because it is not readily attacked by hydroxyl radicals in the troposphere, 1,1,1-trichloroethane may reach the stratosphere, where it could produce oxides of chlorine (ClO_x).

The heart, lung, liver, kidneys, and central nervous system are affected by 1,1,1-trichloroethane. The compound is almost completely eliminated in an unaltered form by the lungs in both rodents and man.

A recent bioassay by NCI did not reveal any significant differences between the incidence of tumors in controls and in exposed animals. An assessment of the carcinogenicity of the compound could not be made because of the abbreviated life spans of the test animals. No statistically significant teratogenic effects were observed in either mice or rats in this study. No information on the mutagenicity of the compound was found in the sources searched.

1,1,1-TRICHLOROETHANE

PART I

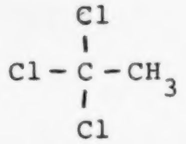
GENERAL INFORMATION

1.1 Identification CAS No.: 000071556
NIOSH No.: KJ29750

1.2 Synonyms and Trade Names

Aerothene TT; chlorothene (inhibited); chlorothene NU; Chlorten; methylchloroform; alpha-trichloroethane (G16)

1.3 Chemical Formula and Molecular Weight



$$Cl-\overset{\displaystyle Cl}{\underset{\displaystyle Cl}{\overset{|}{\underset{|}{C}}}}-CH_3$$

$C_2H_3Cl_3$ Mol. wt. 133.41 (G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless liquid (G21)

1.4.2 Boiling Point: 74.1° C (G22)

1.4.3 Melting Point: -30.41° C (G22)

1.4.4 Absorption Spectrometry:

No information was found in the sources searched.

1.4.5 Vapor Pressure: 100 mm at 20° C (G22)

1.4.6 Solubility: Insoluble in water; soluble in chloroform; soluble in all proportions in alcohol, ether (G22)

1.4.7 Octanol/Water Partition Coefficient

No information was found in the sources searched.

1.5 Production and Use

1.5.1 Production:	440.7 million lb	(1972)	
	458.8 million lb	(1975)	
	631.3 million lb	(1976)	(G24)

1.5.2 Use: As a solvent for cleaning precision instruments; in metal degreasing; as a pesticide; in cold type metal cleaning; in cleaning plastic molds (G21,G23)

Quantitative Distribution:	Percentage
Solvent including metal degreasing and electrical and electronic equipment cleaning	70
Aerosols, solvent for adhesives and polishes, and other uses	15
Exports	15
	100

(G25)

Consumer Product Information:

Category	No. of products containing 1,1,1-trichloroethane	No. of 1,1,1-trichloroethane products in category / Total no. of products in category x100
Cleaning agents and compounds	5	0.28%
Flame retardant chemicals	1	0.17%
Household aerosols	82	2.18%
Chemical deodorizers	1	0.31%
Photographic chemicals	6	1.49%
Solvent based cleaning and sanitizing agents	40	18.35%
Caustics, lyes, and drain cleaners	1	0.44%
Adhesives and adhesive products including glue	10	1.89%

The 146 products surveyed contained an average of 47% 1,1,1-trichloroethane. (G27)

1.6 Exposure Estimates

1.6.1 Release Rate: 285 million lb (G28)

1.6.2 NOHS Occupational Exposure

Rank: 42

Estimated no. of persons exposed: 2,904,000 (G29)

In its criteria document, NIOSH estimated that 100,000 workers in the United States are potentially exposed to 1,1,1-trichloroethane. (5)

1.7 Manufacturers

Dow Chemical Co.
Vulcan Materials Co.
Pittsburg Plate Glass Co.
Ethyl Corp. (G24)

1,1,1-TRICHLOROETHANE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

The high fat solubility and low chemical reactivity of 1,1,1-trichloroethane will tend to cause it to bioaccumulate, but this is offset by its high vapor pressure (100 mm at 20°C) and resultant volatility (G22).

2.2 Impurities and Environmental Degradation or Conversion Products

Impurities found in 1,1,1-trichloroethane include water, hydrochloric acid, and unidentified nonvolatile residues (G14), as well as dioxane, butanol, and ethylene dichloride (G38). Federal specifications provide additional data on the composition of the technical product. For technical, inhibited 1,1,1-trichloroethane, the specification calls for 94.5% purity by weight and 90.0% purity by volume. Individual halogenated impurities must not exceed 0.5%, and total halogenated impurities are limited to 1.0%. The acidity (as HCl) is restricted to 5 ppm and no free halogens are allowed (4).

Although 1,1,1-trichloroethane is very stable, small amounts of stabilizing substances are always added to the commercial product. Patented additives include glycol diesters, ketones, ketols, nitriles, dialkyl sulfoxides, imines, dialkyl sulfides, dialkyl sulfites, tetraethyllead, morpholine, nitroaliphatic hydrocarbons, 2-methyl-3-butyn-2-ol, tert-butyl alcohol, tetrahydrofuran, 1,4-dioxane, sec-butyl alcohol, and monohydric acetylenic alcohols (G17).

1,1,1-Trichloroethane is very stable in the troposphere (2). It reacts very slowly with peroxides, ozone, and the hydroxyl radical with half-lives in excess of 5 years (G14). Possible products include 1,1-dichloroethylene and dichloroacetaldehyde. At pH 7, hydrolysis is very slow ($t_{1/2}$>3,000 hr). The compound is not photoactive (G14). The National Academy of Sciences has reported that 1,1,1-trichloroethane, in view of the exponential growth in its production, ranks third behind Freon 11 and Freon 12 among the major man-made threats to the stratospheric ozone. There is some concern that, because 1,1,1-trichloroethane is not readily attacked by hydroxyl radicals in the troposphere, it may reach the stratosphere, where it could produce oxides of chlorine (ClO_x) (2).

2.3 Acute Toxicity

The acute toxicity of 1,1,1-trichloroethane as reported in the NIOSH Registry of Toxic Effects of Chemical Substances (G16) is given in Table VIII-1.

TABLE VIII-1

ACUTE TOXICITY OF 1,1,1-TRICHLOROETHANE

Parameter	Dosage	Animal	Route
LCLo	27 g for 10 min	Human	Inhalation
"	1,000 ppm	Rat	"
TCLo	350 ppm	Human	"
"	920 ppm for 70 min	"	"
LD50	4,700 mg/kg	Mouse	Intraperitoneal
"	750 mg/kg	Dog	Oral
"	5,660 mg/kg	Rabbit	"
"	9,470 mg/kg	Guinea pig	"

Among the main sites affected by 1,1,1-trichloroethane are the heart, lungs, liver, kidneys, and central nervous system (5). Because of the volatility and uses of the compound, most exposures are by inhalation.

Effects of the inhalation of 1,1,1-trichloroethane on the human heart include decreased blood pressure and bradycardia. Electrocardiograms of patients anesthesized with 1,1,1-trichloroethane show changes in nodal rhythm and premature ventricular contractions. Animals show the following effects: cardiovascular depression, decreased stroke volume, cardiac arrhythmias, tachycardia, and, at very high doses, congestion and fibrillation (5). The results of the individual studies are presented in Table VIII-2.

TABLE VIII-2

ACUTE EFFECTS OF INHALATION OF 1,1,1-TRICHLOROETHANE ON THE CARDIOVASCULAR SYSTEM (4,5)

Animal	Exposure	Response	Reference Cited
Dog	125,000 ppm for 1.5-6 min	Abrupt drop in blood pressure; ventricular fibrillation in one dog on second exposure; gross congestion in all tissues; heart cell necrosis	14
"	8,000 ppm for 5 min	Sharp decrease in peripheral resistance followed by decreased stroke volume, heart rate, and myocardial contractility	15
"	5,000 ppm for 5 min	Cardiac sensitization to epinephrine	16
"	2,500 ppm for 5 min	No cardiac sensitization to epinephrine	16
Rhesus monkey	25,000 ppm for 5 min	Cardiac arrhythmias; myocardial depression; tachycardia	17
Rabbit	6,250 ppm for 10 min	Cardiovascular depression	18
Human and dog	Anesthesia (unspecified)	Little effect on electrocardiograms, but consistently decreased blood pressure	6*, 13

*primary source

Histological examination of the lungs of animals acutely exposed to 1,1,1-trichloroethane revealed congestion and inflammatory changes (5). The pulmonary effects of 1,1,1-trichloroethane are given in Table VIII-3.

TABLE VIII-3

ACUTE EFFECTS OF INHALATION OF 1,1,1-TRICHLOROETHANE ON THE LUNGS (4,5)

Animal	Exposure	Response	Reference Cited
Human (female)	Several days intentional inhalation	Death; autopsy revealed congestion of the bronchial vessels with thick yellowish-brown secretions; congestion throughout the lungs	19
Human	4 hr cleaning metal parts with 1,1,1-trichloroethane	Death; autopsy revealed congested edematous lungs	8
Mouse	100 ppm for 2 hr/day 9 exposures on alternate days	Lung congestion	20

The effects on the liver of acute inhalation exposure to 1,1,1-trichloroethane, summarized in Table VIII-4, are increases in weight accompanied by fatty changes and hemorrhagic necrosis (5).

TABLE VIII-4

ACUTE EFFECTS OF INHALATION OF 1,1,1-TRICHLOROETHANE ON THE LIVER AND KIDNEYS (4,5)

Animal	Exposure	Response	Reference Cited
Human	2 hr anesthesia	No effect on SGPT activity in five subjects and therefore presumably no hepatotoxicity	13

TABLE VIII-4 (continued)

Animal	Exposure	Response	Reference Cited
Human	0-2,650 ppm for 15 min	Positive urinary urobilinogen	10
"	500 ppm 7 hr/day for 5 days	No evidence of liver or kidney injury	21
Rat	18,000 ppm for 2 hr	Increased kidney weight	22
"	12,000 ppm for 7 hr	Increased liver weight, fatty liver changes; congestion and hemorrhagic necrosis; increased kidney weight	22
"	8,000 ppm for 7 hr	Fatty changes in liver	22

The effects of 1,1,1-trichloroethane inhalation on the kidneys have not been studied as extensively as the effects of the chemical on the liver, but congestion, increase in kidney weight, and definite disturbances in renal function have been reported in experimental animals (5). The effects on the kidneys have also been presented in Table VIII-4.

The most harmful effects of inhaling 1,1,1-trichloroethane apparently are central nervous system disorders, including anesthesia, impairment of perceptual speed, delayed reaction time, decreased manual dexterity, and disturbed equilibrium (5). These effects are given in Table VIII-5.

TABLE VIII-5

ACUTE EFFECTS OF INHALATION OF 1,1,1-TRICHLOROETHANE ON THE CENTRAL NERVOUS SYSTEM (5)

Animal	Exposure	Response	Reference Cited
Human	10,000-26,000 ppm	Induction of anesthesia usually within 2 min	23
"	6,000-22,500 ppm	Maintenance of anesthesia	23
"	0-2,650 ppm for 15 min	2 of 7 exposed subjects unable to stand	10
"	1,740-2,180 ppm	Disturbed equilibrium	7
"	1,000 ppm for 70-75 min	Impaired coordination and equilibrium	7
"	500 ppm for 450 min	Reflexes and equilibrium undisturbed	7
"	500 ppm for 3 hr	Balance and coordination not affected	10
"	450 ppm for 8 hr	Decreased perceptive capabilities under stress conditions	24
"	350 ppm for 2 hr	Perceptual speed, reaction times, and manual dexterity impaired	25
"	250 ppm for 2 hr	Perceptual speed, reaction times, and manual dexterity not impaired	25
Rat	18,000 ppm for 5 min	"Helpless"	22
"	18,000 ppm for 3 hr	Unconscious	22
"	10,000 ppm for 1-2 min	Decreased activity	22

TABLE VIII-5 (continued)

Animals	Exposure	Response	Reference Cited
Rat	10,000 ppm for 10 min	"Helpless"	22
"	10,000 ppm for 3 hr	Semiconscious	22
"	5,000 ppm for 1 hr	Mild narcotic effect	22
Rat and cat	180-900 ppm for 4 hr	Threshold for altering conditioned reflex activity	26
Monkey	5,000 ppm for 1 hr	Slight ataxia	22
"	5,000 ppm for 5 hr	Trembling of hands and forearms	22
Rabbit	16,850 ppm for 5 min	Increased EEG activity	18
"	16,850 ppm for more than 5 min	Decreased EEG activity	18

Six fatal cases of 1,1,1-trichloroethane inhalation in four separate incidents were reviewed by Stahl et al. (8). All six deaths resulted from acute inhalation of the compound at high concentrations. The autopsy reports on the victims can be summarized as follows:

1. Liver, lungs, spleen, kidneys, and brain congested; lungs moderately edematous; brain anoxic.
2. Skin moderately cyanotic; brain, liver, kidneys, and spleen moderately congested; lungs markedly edematous with signs of aspiration of the stomach contents.
3. Fatty liver with centrilobular fatty change; brain, spleen, and kidneys congested and lungs congested and edematous.

4. Bullous lesions and focal denudation of buttock skin; congested and edematous lungs with aggregates of polymorphonuclear leukocytes.

In one study, the inhalation LT50 was reported as follows (1):

Parameter	Dosage	Animal
LT50	18,000 ppm for 3 hr	Rat
"	14,000 ppm for 7 hr	"

In addition to the numerous studies on 1,1,1-trichloroethane by inhalation, a few have been done by other routes.

1,1,1-Trichloroethane applied as a 5% solution in corn oil to the eyes of rabbits produced chemosis and hyperemia in the conjunctivae (6, as reported in 5).

A single undiluted application of 1,1,1-trichloroethane to rabbit eyes was reported by Torkelson et al. (7, as reported in 5) to cause slight conjunctival irritation but essentially no corneal damage. In the same study, slight eye irritation was reported in one of four human subjects exposed to 1,1,1-trichloroethane vapor at 900-1,000 ppm.

Only a slight reddening and scaliness of the skin were reported to develop when a pad of cotton saturated with 1,1,1-trichloroethane was bandaged to the shaved belly of a rabbit 10 times in 12 days. When applied to abraded skin, 1,1,1-trichloroethane had no significant effects on the healing process (7, as reported in 5).

In a human, the ingestion of an unspecified quantity of 1,1,1-trichloroethane produced kidney damage, as evidenced by elevated serum bilirubin and the presence of red blood cells and protein in the urine (10, as reported in 5).

An intraperitoneal dose of the compound at 3,800 mg/kg had no effect on liver triglyceride levels in rats, but at higher doses (nearly lethal) the levels were raised (11, as reported in 4).

Intraperitoneal doses of 1,1,1-trichloroethane at 3,400 mg/kg produced swelling of the proximal convoluted tubules of the kidneys in a significant number of mice (12, as reported in 4).

2.4 Other Toxic Effects

Numerous long-term inhalation studies have been performed using 1,1,1-trichloroethane. In most of the studies no significant major toxic effects were observed. The results are summarized in Table VIII-6.

Chronic oral studies were performed using rats and mice during the NCI carcinogenicity bioassay (27). 1,1,1-Trichloroethane was administered by gavage once a day, 5 days/week for 78 weeks. Rats were given 750 or 1,500 mg/kg/day and mice were given varied doses averaging 2,807 or 5,615 mg/kg/day. As the study progressed, increasing numbers of exposed rats exhibited urine staining on the fur. The exposed rats also developed respiratory problems characterized by wheezing, rapid or labored breathing, nasal discharge, and a hunched appearance. A smaller number of controls exhibited the same symptoms. The exposed rats more often than the controls developed a bloody discharge or crust around the eyes. The survival rate of the exposed rats was significantly lower than that of the controls and was dose dependent. In the first year, 7/20 of the control rats, 56/100 of the low-dose group, and 57/100 of the high-dose group died. The mice exhibited no significant

TABLE VIII-6

EFFECTS OF 1,1,1-TRICHLOROETHANE ON HUMANS AND ANIMALS AFTER PROLONGED OR REPEATED INHALATION

Animal	Number	Exposure	Response	Reference Cited
Human (males)	11	500 ppm 6.5-7 hr/day for 5 days	Headache; eye, nose, and throat irritation (only in two subjects); body chemistry within normal range	21
Monkey	4	250 ppm and 1,000 ppm for 14 wk (continuous)	No significant changes in body chemistry (HCB, HGB, RBC, WBC, Na, K, alkaline phosphatase, SGOT, SGPT, or serum triglycerides); no lesions attributable to exposure at either dose level found in pathological examination	28
"	1	3,000 ppm 7 hr/day, 5 days/wk (53 exposures) for 74 days	No pathological changes in major organs examined	29
"	3	2,700 ppm 8 hr/day, 5 days/wk for 6 wk	No adverse effects	30
"	3	450 ppm for 90 days (continuous)	Nonspecific lung inflammation	30
"	3	165 ppm 90 days (continuous)	Sporadic lung congestion	30
Dog	8	250 ppm and 1,000 ppm for 14 wk (continuous)	No significant changes in body chemistry; no lesions attributed to exposure	28

TABLE VIII-6 (continued)

Animal	Number	Exposure	Response	Reference Cited
Dog	8	2,700 ppm 8 hr day, 5 days/wk for 6 wk	Slight leukopenia	30
"	2	450 ppm for 90 days (continuous)	Nonspecific lung inflammation	30
"	2	165 ppm for 90 days (continuous)	Sporadic lung congestion	30
Rabbit	2	5,000 ppm 7 hr/day, 5 days/wk (31 exposures) for 44 days	Slight depression in growth rate; all other variables normal or negative	31
Rat	5-7	5,000 ppm 7 hr/day, 5 days/wk (47-48 exposures) for 66-67 days	Ataxia, lethargy; retardation of growth rate in females through week 2, then recovery to control levels	30
"	5-7	2,700 ppm 8 hr/day, 5 days/wk (30 exposures)	No adverse effects	30
"	15	450 ppm for 90 days (continuous)	Normal	30
"	15	165 ppm for 90 days (continuous)	Nodules on a lower lung lobe in one rat	30

TABLE VIII-6 (continued)

Animal	Number	Exposure	Response	Reference Cited
Rat	15	165 ppm for 90 days (continuous)	Sporadic lung congestion and pneumonitis	30
"	40	250 and 1,000 ppm for 14 wk (continuous)	Liver/body weight ratio significantly increased at 1,000 ppm	28
Guinea pig	5-12	650-1,000 ppm 7 hr/day, 5 days/wk for 29-93 days	At 5,000 ppm, remarkable decrease in growth rate of males and females and slight centrilobular fatty infiltration in liver but no necrosis; slight testicular degeneration; at 3,000 ppm slight centrilobular fatty infiltration, with small fat-staining globules in central hepatocytes	29
Mouse	180	250 ppm and 1,000 ppm for 14 wk (continuous)	Significant increase in fat droplets in centrilobular hepatocytes at 1,000 ppm;liver triglycerides elevated throughout exposure at 1,000 ppm but returned to normal after 2 wk	28

TABLE VIII-6 (continued)

Animal	Number	Exposure	Response	Reference Cited
Mouse	10	250 ppm and 1,000 ppm for 14 wk (continuous)	At 1,000 ppm, relative and absolute liver weight significantly greater; triglyceride level elevated; at 1,000 ppm, centrilobular hepatocyte hypertrophy due to small cytoplasmic vacuoles; occasional cell with "balloon" degeneration, or extensive enlargement due to cytoplasmic vacuolization with pycnotic nuclei; peak fat accumulation; focal necrosis at week 10, with acute inflammatous exudate (mainly neutrophils)	32
Rat	19	875 ppm and 1,750 ppm 6 hr/day, 5 days/wk for 52 wk	Death rate same as in controls; neutrophilia in 6% and lymphocytopenia in 7% of males at 1,750 ppm; lymphocytosis in 13% of females at both levels	27

signs other than a dose-dependent reduction in weight gain and, in females, a dose-dependent increase in death rate.

A Threshold Limit Value (TLV) of 1,900 mg/m^3 has been set for 1,1,1-trichloroethane (G11).

2.5 Carcinogenicity

Results of NCI bioassay studies on technical grade 1,1,1-trichloroethane containing 3% para-dioxane have recently been reported (27). Groups of rats and mice were fed 1,1,1-trichloroethane at two concentrations 5 days/week for 78 weeks. Rats were fed 750 and 1,500 mg/kg/day, while mice received doses averaging 2,807 and 5,616 mg/kg/day. A variety of neoplasms was reported in the test animals, but none occurred at frequencies significantly higher than they did in the controls. A few of the malignant neoplasms were observed only in the exposed rats--papillary cystadenocarcinoma in the subcutis of 1/50 of the high-dose females, transitional-cell carcinoma of the bladder in 1/50 of the high-dose males, malignant brain glioma in 1/48 of the low-dose males, and mesenteric metastatic osteosarcoma in 1/50 of the high-dose females. Only 3% of the exposed rats survived until the end of the experiment. In the exposed mice, no neoplasms occurred that had not been previously observed as spontaneous lesions.

NCI concluded that the neoplasms observed were not attributable to the test compound because there was no apparent relationship between the dosage groups, the sex, the species, the type of neoplasm, or the site of occurrence. Even if such a relationship could have been established, according to NCI, the abbreviated life spans of both the rats and the mice made it inappropriate to assess the carcinogenicity of 1,1,1-trichloroethane on the basis of this bioassay (27).

2.6 Mutagenicity

No information on the mutagenicity of this compound was found in the sources searched.

2.7 Teratogenicity

The effects of 1,1,1-trichloroethane on the embryonic and fetal development of rats and mice were studied. at a vapor concentration of 875 ppm (a concentration two times the maximum allowable excursion limit for human industrial exposure, as defined by ACGIH in 1976). Groups of pregnant Sprague-Dawley rats and Swiss-Webster mice were exposed to this solvent 7 hours daily on days 6-15 of gestation. An increase in liver weight was reported to be the only significant maternal, fetal, or embryonic toxic effect in rats at 875 ppm. There were no significant findings reported in mice. Although the authors concluded that the compound had no statistically significant teratogenic effects in either mice or rats, certain soft tissue or skeletal abnormalities occurred in the exposed animals that did not occur in the controls. These abnormalities included one litter of mice with short tails and one with cleft palates. In rats, two litters with extra vertebrae were found (33, as reported in 5).

2.8 Metabolic Information

Because of its volatility and biological stability, 1,1,1-trichloroethane is almost completely eliminated unaltered through the lungs in both rodents and man. If metabolized, the compound is transformed into trichloroacetic acid and trichloroethanol in a dose-dependent manner (G10).

The pulmonary excretion of ^{38}Cl-labeled 1,1,1-trichloroethane was measured in humans for 1 hour after the inhalation of a single breath. In the first hour, 44% of the dose was excreted (9, as reported in 4).

Hake et al. (1) injected rats intraperitoneally with labeled 1,1,1-trichloroethane at about 700 mg/kg. After 25 hours, 98.7% of the initial dose was excreted unchanged in the expired air, and 0.5% was converted to $^{14}CO_2$. Much of the remainder appeared as the glucuronide of 2,2,2-trichloroethanol in the urine. At this dose level the metabolism of 1,1,1-trichloroethane apparently proceeds through an initial oxidation to trichloroethanol, which is then oxidized to trichloroacetic acid (4). Chloroacetic acid, S-carboxymethyl cysteine, and two conjugated diacetic acids were found in the urine of animals after exposure to 1,1,1-trichloroethane under unspecified conditions (G10).

A secondary source reports that 1,1,1-trichloroethane is not known to be metabolized by aerobic or anaerobic microorganisms (3, as reported in 4).

2.9 Environmental Release and Ecological Effects

SRI International estimated that in 1972, when 440.7 million pounds of 1,1,1-trichloroethane were produced in the United States, 6.6 million pounds were lost to the environment during production and 278 million were released to the environment in its commercial use pattern (G14). The National Academy of Sciences has reported that 1,1,1-trichloroethane poses a major threat to the stratospheric ozone (2). (See Section 2.2.)

1,1,1-Trichloroethane was found as a contaminant at concentrations of 3-10 μg/kg in foods sampled in the United Kingdom (3, as reported in 4).

The compound has an Aquatic Toxicity Rating (96-hr TLm, species unspecified) of 100-10 ppm, which is considered slightly toxic (G16).

2.10 Current Testing

No information was found in the sources searched.

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APPENDIX B

KEY TO ABBREVIATIONS

TCLo	Lowest Published Toxic Concentration The concentration of a substance in air that has been reported to produce any toxic effect in animals or humans over a given exposure time
TDLo	Lowest Published Toxic Dose The lowest dose of a substance introduced by any route other than inhalation over a given period of time that has been reported to produce any toxic effect in animals or humans
LCLo	Lowest Published Lethal Concentration The lowest concentration of a substance in air, other than an LC50, that has been reported to have killed humans or animals over a given exposure time
LDLo	Lowest Published Lethal Dose The lowest dose of a substance, other than an LD50, introduced by any route other than inhalation over a given period of time that has been reported to have killed humans or animals
LC50	Median Lethal Concentration The concentration of a test material that kills 50% of an experimental animal population within a given period of time
LD50	Median Lethal Dose The dose of a test material, introduced by any route other than inhalation, that kills 50% of an experimental animal population within a given period of time
LT50	Median Lethal Response Time Statistical estimate of the time from exposure to the death of 50% of the organisms in a population subjected to a toxicant under specified conditions
MLD	Median Lethal Dose The dose of a test material, introduced by any route other than inhalation, that kills 50% of an experimental animal population within a given period of time

TLm	Median Tolerance Limit The concentration of a test material at which 50% of an experimental animal population survive for a specified time period
TLV	Threshold Limit Value The airborne concentration of a substance to which nearly all workers may be repeatedly exposed day after day without adverse effect
TWA	Time-Weighted Average The average concentration of a substance for an 8-hour workday or 40-hour workweek

NOHS Occupational Exposure:

Rank: A number representing the chemical's place in a list ranking approximately 7,000 occupational hazards according to the number of workers exposed; the lower the number, the more common the hazard

Estimated no. of persons exposed: This figure includes full- and part-time workers. For hazards ranked 1-200, the figure given is a projection to national statistics by NIOSH in its National Occupational Hazard Survey (NOHS). For the remaining hazards, the number given in the NOHS was multiplied by a fixed muber to give a rough estimate of national exposure. The fixed number (30) is derived from the statistical sampling technique used in the NOHS.

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